REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and the reasons that follow.

Status of the Claims

Claim 64 is amended to recite specific embodiments. Specifically, claim 64 is amended to clarify that the matrix composition is an erodible composition (see, e.g., paragraph [0051]) that comprises a mixture of components (a) – (c) (see, e.g., paragraph [0259]); that the erodable matrix composition comprises a polyethylene glycol, a polyethylene oxide and/or a block copolymer of ethylene oxide and propylene oxide (as previously recited in claim 82); that the erodable matrix composition is provided with a single coating (see, e.g., paragraph [0263] – [0264]), and that the composition exhibits a zero order release profile and about 75% w/w of the opioid is released from the composition within 4-10 hours when tested in a Dissolution Test in accordance with USP 24, NF 19, (711), Dissolution, apparatus 2, equipped with a paddle, with or without sinkers (see, e.g., paragraphs [0091], [0257]).

Claim 82 is canceled. Claims 83-84 and 88 are amended to correct clerical issues.

These amendments do not introduce and new matter and are made without prejudice or disclaimer. Applicant reserves the right to pursue any canceled subject matter in one or more continuing applications with the same priority rights as the instant application.

Applicant respectfully urges entry of these amendments after final because they are believed to place the application in condition for allowance.

Upon entry of these amendments, claims 64-66, 69-79 and 83-88 will be pending. These claims are presented for reconsideration.

The Patent Office Interview

Applicant thanks the Examiner for the courtesies extended during the Patent Office Interview on May 3, 2011. Applicant's Statement of the Substance of the Interview is set forth here. As reflected in the Examiner Interview Summary, Applicant's representative discussed the teachings of Rao, Wong, DePrince and Sackler, and explained that they operate on different principles from each other and from the claimed compositions. Applicant's representative also discussed proposed claim amendments, reflected above, to further clarify the claimed compositions and further distinguish the cited references. These points are explained in more detail below.

Rejections under 35 USC § 103

The Office Action maintains the four obviousness that were set forth previously, based on (i) Rao; (ii) Wong and Rao; (iii) DePrince and Rao and (iv) Sackler and Rao. Applicant respectfully traverses these rejections in as much as they may be applied to the instant claims.

As reflected in independent claim 64, the instant claims are directed to methods for treating a patient suffering from pain that is sensitive to an opioid comprising orally administering such opioid in a controlled release pharmaceutical composition, comprising an erodible matrix composition comprising a mixture of: (a) a polymer or a mixture of polymers, (b) an opioid, and optionally, (c) one or more pharmaceutically acceptable excipients. The erodible matrix composition comprises a polyethylene glycol, a polyethylene oxide and/or a block copolymer of ethylene oxide and propylene oxide, and does not comprise polyethylene glycol 2000 monostearate or polyethylene glycol 400 monostearate. The erodible matrix composition is provided with a single coating that is substantially insoluble in and impermeable to aqueous media, the coating comprising one or more polymers selected from the group consisting of ethylcellulose, cellulose acetate, polyamide, polyethylene, polyethylene terephthalate, polypropylene, polyurethane, polyvinyl acetate, polyvinyl chloride, silicone rubber, latex, polyhydroxybutyrate, polyhydroxyvalerate, teflon, polylactic acid or polyglycolic acid and copolymers thereof, ethylene vinyl acetate (EVA), styrene-butadienestyrene (SBS) and styrene-isoprene-styrene (SIS). The coating has two openings that expose at least one surface of the matrix, thereby allowing controlled release of the opioid by erosion of said matrix surface. The

composition exhibits a zero order release profile and about 75% w/w of the opioid is released from the composition within 4-10 hours when tested in a Dissolution Test in accordance with USP 24, NF 19, (711), Dissolution, apparatus 2, equipped with a paddle, with or without sinkers. Such methods are not taught or suggested by the cited references.

(i) Rao (US 2003/0203055)

Rao is directed to methods of treating visceral pain syndrome using a specific active agent, milnacipran. The Office Action cites Examples 6 and 10 of Rao as teaching compositions that read on specific elements of the recited compositions. However, no teaching in Rao suggests the recited compositions as a whole.

As discussed during the Patent Office Interview, Example 6 of Rao discloses two embodiments:

The first embodiment is based on U.S. 6,245,357 (copy attached for the Examiner's convenience), and comprises a matrix comprising an active ingredient in a polyethylene oxide carrier that is surrounded by (i) an interior wall and (ii) an exterior wall with "an exit." As taught in the '357 patent, the "exit" ("passageway") is comprised of an erodible material. *See, e.g.,* '357 patent, col. 10, line 61.

As taught in the '357 patent, this composition achieves controlled delivery by osmotic pump action. *See, e.g.,* '357 patent, col. 2, lines 50-55; col. 11, lines 58-67. As reflected in the '357 patent, the presence of two walls is essential to the function of the disclosed compositions. *See, e.g.*, '357 patent, col. 2, lines 38-49. Thus, this embodiment does not teach or suggest a composition as claimed, where the matrix composition is provided with a single coating.

The second embodiment of Example 6 of Rao comprises an active ingredient surrounded by (1) a coating with a passage former and (2) a wall that surrounds the coat that protects the composition from lipids in the GI tract. This embodiment does not teach or suggest a composition as claimed, where the matrix composition is provided with a single coating. Moreover, there is no teaching or suggestion that any coating of this embodiment should have two openings that expose at least one surface of the matrix. To the contrary, the

teaching of an outer wall to protect the composition from lipids in the GI tract teaches away from using a coating with two openings, since the openings would expose the composition.

Example 10 of Rao is based on U.S. Patent 5,882,682 (copy attached for the Examiner's convenience), and comprises a compressed core that includes the active ingredient and a polymer which forms "gelatinous microscopic particles upon hydration." The core is surrounded by an insoluble coating which contains apertures exposing the core. As taught in the '682 patent, during use the gelatinous microscopic particles form a dispersion comprising the active agent that provides controlled delivery. *See, e.g.*, '682 patent, col. 3, lines 38-48. Thus, as discussed in the Patent Office Interview, Example 10 of Rao does not teach or suggest a composition comprising an erodible matrix as recited in the instant claims.

The Office Action cited Example 10 of Rao for teaching a coating with multiple openings, but the skilled artisan would not have combined isolated aspects of this example with any of the embodiments disclosed in Example 6 of Rao. As discussed during the Patent Office Interview, the compositions of Example 10 operate on a different principle that those of Example 6, and both operate on different principles than the recited compositions. Indeed, the '682 patent emphasizes that its controlled delivery does not depend on solubility, diffusion, or an extra tablet suprastructure. *See, e.g.*, '682 patent, col. 3, lines 53-67.

Thus, the skilled artisan would not have had any reasonable expectation that selecting and combining isolated aspects of the different compositions of Examples 6 and 10 would result in a composition that achieves controlled delivery. For example, Example 10 relies on the gel-forming polymer to provide controlled release. Since Example 6 does not include such a polymer, the skilled artisan would not expect to be able to use a coating as described in Example 10 with a matrix as described in Example 6 while still achieving controlled delivery, let alone any reasonable expectation that the delivery and dissolution profiles recited in the instant claims could be achieved.

For at least these reasons, Applicant respectfully urges reconsideration and withdrawal of the rejection based on Rao.

(ii) Wong (U.S. 4,824,675) and Rao

Wong teaches a dispenser for delivering "tiny pills" to an environment of use, such as in the GI tract. According to Wong, the dispenser consists of an internal lumen that contains a carrier means consisting of a carrier and tiny pills of the active agent, which carrier means is surrounded by a wall. See, e.g., Wong, col. 6, lines 5-7. A passageway or opening connects the outside of the dispenser with the lumen. *Id.*

As discussed during the Patent Office Interview, the "tiny pills" of Wong consist of an active agent core surrounded by a wall. See, e.g., Wong, col. 14, lines 64-67. Thus, Wong does not teach a matrix composition comprising a mixture of (a) a polymer or a mixture of polymers, (b) an opioid, and optionally, (c) one or more pharmaceutically acceptable excipients, as recited in the instant claims—Wong's active agent is not a component of any mixture. Moreover, the coating ("wall") that is present on Wong's "tiny pills" does not have any openings. These are a few of the many differences between Wong and the recited compositions.

Combining Rao with Wong does not remedy the deficiencies of Wong for the reasons set forth above. That is, neither Wong nor Rao teach or suggest a composition as claimed. Moreover, the skilled artisan would not have had a reason to select and combine isolated components of the compositions of Wong and Rao, since they operate on different principles, nor would the skilled artisan have had any reasonable expectation of achieving a controlled release composition that exhibits the delivery and dissolution profiles recited in the instant claims.

Applicant therefore respectfully urges reconsideration and withdrawal of the rejection based on Wong and Rao.

(iii) DePrince (U.S. 4,898,733) and Rao

DePrince discloses a layered, compression molded device for the sustained release of an active agent. The disclosed device comprises a body fluid contacting layer that is compression molded onto a non-body fluid contacting layer, while an outer barrier layer made of an impermeable material surrounds the inner layers.

As noted previously, DePrince's multi-layered compression molded system does not teach or suggest the claimed composition comprising an active agent matrix provided with a

single coating. The differences between the recited compositions and those of DePrince are underscored by their different deliver profiles. For example, DePrince's composition releases drug over many days. See, e.g., DePrince, Figures 3-4. Thus, DePrince does not teach or suggest a composition wherein about 75% w/w of the opioid is released within 4-10 hours, as recited in the instant claims.

Combining Rao with DePrince does not remedy the deficiencies of DePrince, for the reasons set forth above. That is, neither DePrince nor Rao teach or suggest a composition as claimed. Moreover, the skilled artisan would not have had a reason to select and combine isolated components of the compositions of DePrince and Rao, since they operate on different principles, and would not have had any reasonable expectation of achieving a controlled release composition that exhibits the delivery and dissolution profiles recited in the instant claims.

For at least these reasons, Applicant respectfully urges reconsideration and withdrawal of the rejection based on DePrince and Rao.

(iv) Sackler (U.S. 5,478,577) and Rao

Sackler is cited for teaching a method for effective pain management using an oral dosage formulation that is allegedly capable of achieving the pharmacokinetic profiles recited in claims 69-78. As discussed during the Patent Office Interview, however, Sackler teaches compositions that achieve first order delivery. *See, e.g.,* Sackler, col. 5, lines 51-55. Thus, Sackler does not teach or suggest a composition that achieves zero order delivery as recited in the claims.

As discussed during the Patent Office Interview, Sackler discloses two distinct embodiments:

The first embodiment is described at columns 7-11, and relates to active agent-coated beads that are provided with a coating (preferably acrylic) that may include openings. This embodiment does not teach or suggest a matrix composition comprising a mixture of (a) a polymer or a mixture of polymers, (b) an opioid, and optionally, (c) one or more pharmaceutically acceptable excipients, as recited in the instant claims—the active agent is not a component of any mixture. .

The second embodiment is described at columns 11-13, and relates to a multi-particulate controlled-release matrix comprising active agent and (i) a hydrophilic polymer, (ii) a digestible long chain hydrocarbon material and (iii) a polyalkylene glycol. This product is formed by granulation, spheronization or pelletization, and is not provided with a coating. Thus, this embodiment does not teach or suggest a controlled release composition as recited in the instant claims, which comprises an erodible matrix provided with a coating.

Combining Rao with Sackler does not remedy the deficiencies of Sackler, for the reasons set forth above. That is, neither Sackler nor Rao teach or suggest a composition as claimed. Moreover, the skilled artisan would not have had a reason to select and combine isolated components of the compositions of Sackler and Rao, since they operate on different principles, and would not have had any reasonable expectation of achieving a controlled release composition that exhibits the delivery and dissolution profiles recited in the instant claims, particularly where Sackler teaches a different delivery profile.

Applicant therefore respectfully urges reconsideration and withdrawal of the rejection based on Sackler and Rao.

CONCLUSION

Applicant believes that the application is in condition for allowance, and favorable reconsideration is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance prosecution, or if any issues remain that might be resolved by telephone.

Respectfully submitted,

Date May 19, 2011

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4094
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff
Attorney for Applicant
Registration No. 37,288

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, then the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

US005882682A

United States Patent [19]

Rork et al.

[11] **Patent Number: 5,882,682**

[45] **Date of Patent: *Mar. 16, 1999**

[54] **CONTROLLED RELEASE SIMVASTATIN DELIVERY DEVICE**

[75] Inventors: **Gerald S. Rork; James D. Pipkin,** both of Lawrence, Kans.

[73] Assignee: **Merck & Co., Inc.,** Rahway, N.J.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,366,738.

[21] Appl. No.: **817,129**

[22] PCT Filed: **Oct. 19, 1995**

[86] PCT No.: **PCT/US95/13693**

§ 371 Date: **Aug. 1, 1997**

§ 102(e) Date: **Aug. 1, 1997**

[87] PCT Pub. No.: **WO96/12478**

PCT Pub. Date: **May 2, 1996**

Related U.S. Application Data

[63] Continuation of Ser. No. 327,083, Oct. 21, 1994, Pat. No. 5,543,154, which is a continuation-in-part of Ser. No. 118,836, Sep. 8, 1993, Pat. No. 5,366,738, which is a continuation of Ser. No. 902,188, Jul. 29, 1992, abandoned, and a continuation-in-part of Ser. No. 815,304, Dec. 27, 1991, abandoned.

[51] **Int. Cl.**[6] **A61K 9/24**

[52] **U.S. Cl.** **424/473**; 424/479; 424/480; 424/489

[58] **Field of Search** 424/473, 479, 424/480, 489

[56] **References Cited**

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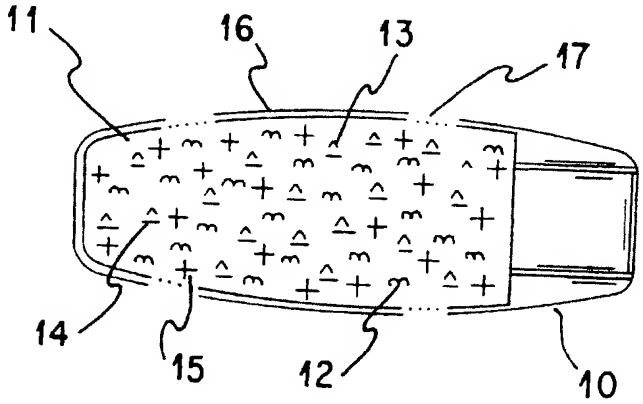
Primary Examiner—D. Gabrielle Brouillette

Attorney, Agent, or Firm—Carol S. Quagliato; Melvin Winokur

[57] **ABSTRACT**

Controlled delivery of a beneficial agent in a dispersion is provided using (i) a compressed core which contains the beneficial agent, a polymer which forms gelatinous microscopic particles upon hydration, and if desired, an agent to modulate the hydration; and (ii) a water insoluble coating which adheres to and surrounds the core and contains apertures which provide an area for the hydration and release of the dispersion. The release rate of the beneficial agent is a function of the number and size of the apertures in the coating.

28 Claims, 7 Drawing Sheets



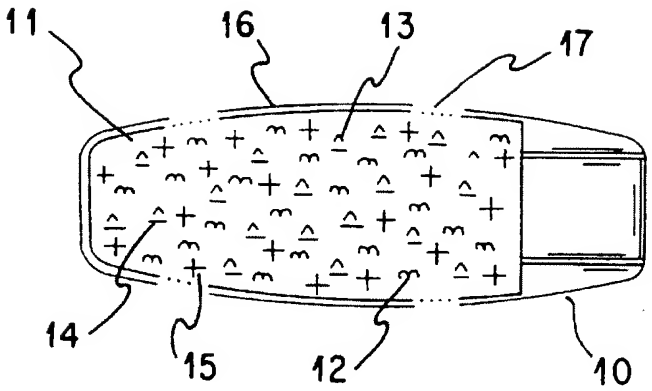
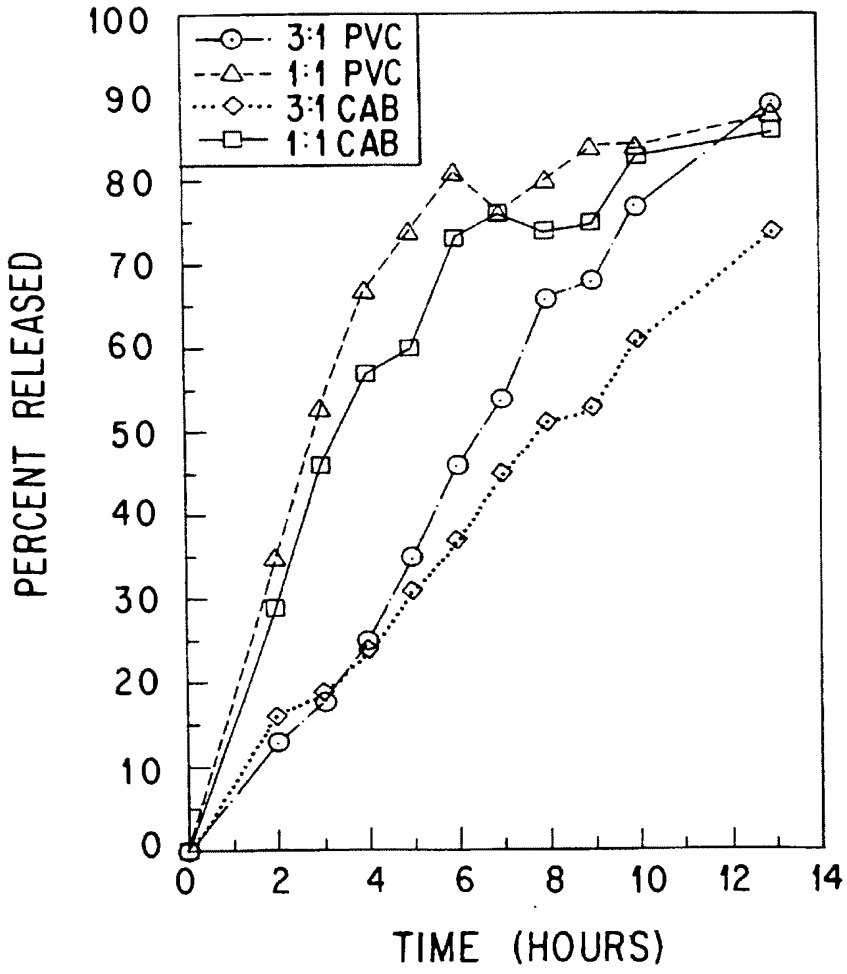


FIG. 1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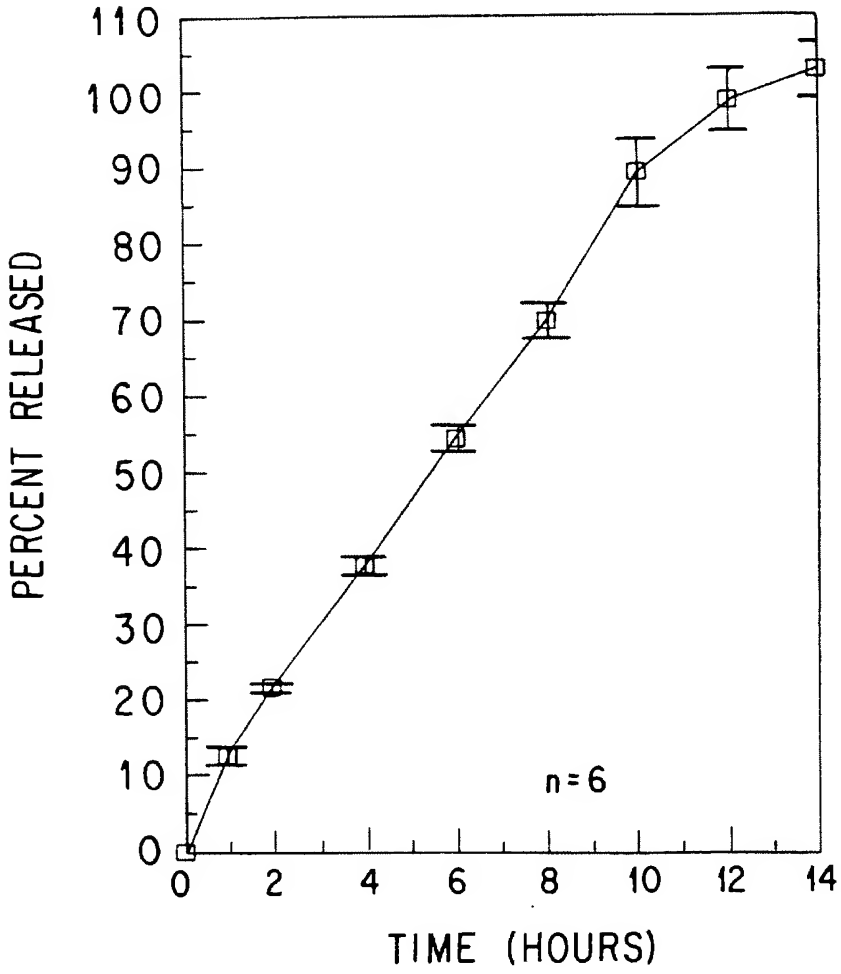
12
14

FIG.2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10
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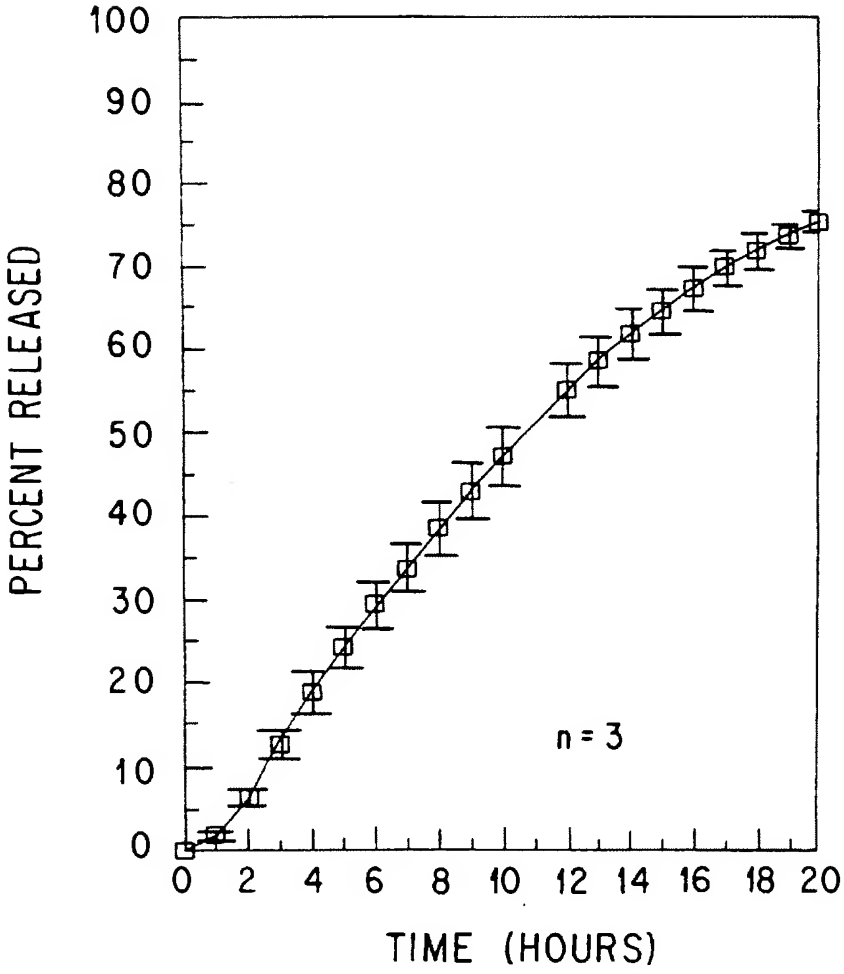
TIME (HOURS)

FIG. 3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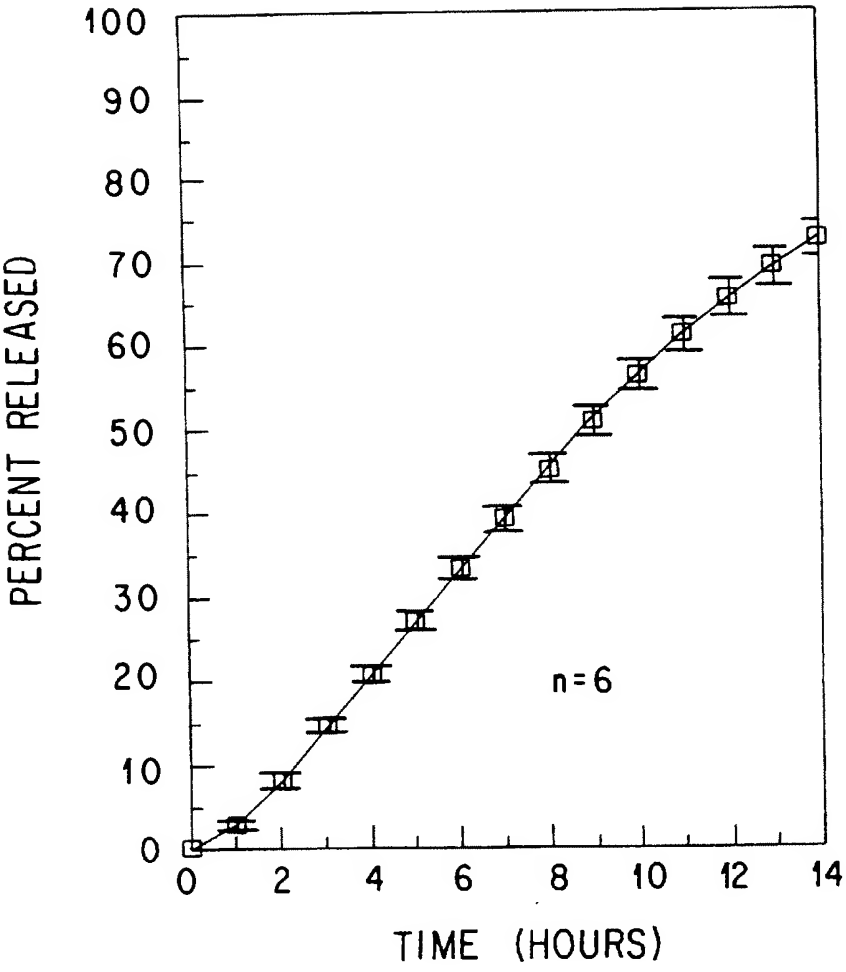
TIME (HOURS)
n = 3

FIG. 4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TIME (HOURS)
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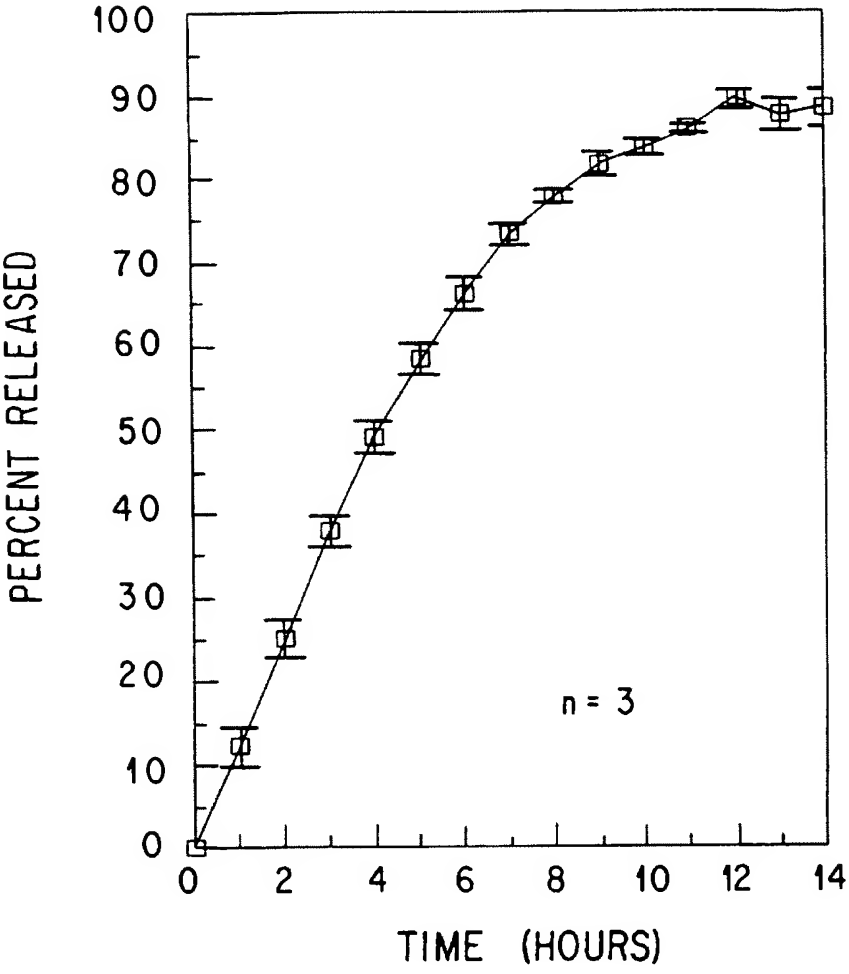
FIG. 5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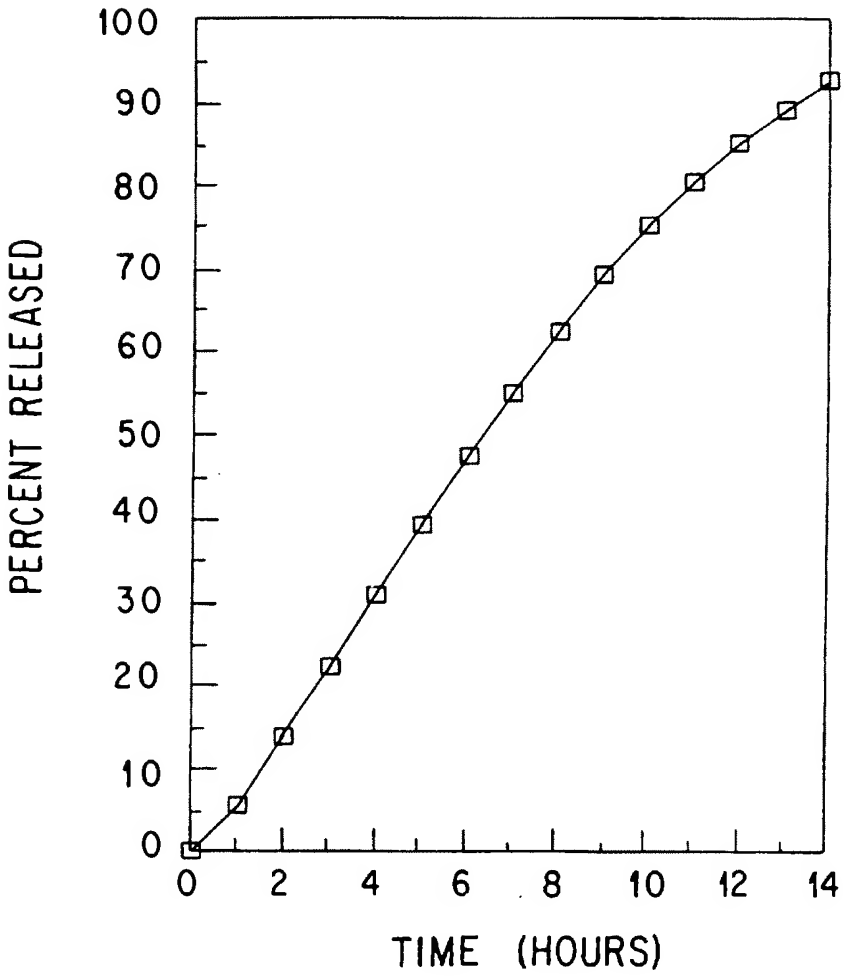
TIME (HOURS)
n = 3

FIG. 6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14
TIME (HOURS)

FIG. 7

CONTROLLED RELEASE SIMVASTATIN DELIVERY DEVICE

RELATED APPLICATIONS

In accordance with 35 USC 371, this application is a continuation of PCT/US95/13693, which was internationally filed Oct. 19, 1995, and itself is a continuation of U.S. Ser. No. 08/327,083, filed Oct. 21, 1994, now issued as U.S. Pat. No. 5,543,154, which itself is a continuation-in-part of U.S. Ser. No. 08/118,836, filed Sep. 8, 1993, now issued as U.S. Pat. No. 5,366,738, which itself is a continuation of U.S. Ser. No. 07/902,188, filed Jul. 29, 1992, now abandoned, and itself is a continuation-in-part of U.S. Ser. No. 07/815,304, filed Dec. 27, 1991, now abandoned.

FIELD OF THE INVENTION

This invention pertains to both a useful and novel drug-delivery device for dispensing a drug to an environment of use. Particularly, the invention pertains to a system that releases a drug in a controlled fashion, by creating gelatinous microscopic particles of polymer gel and in so doing, generates a dispersion of drug among the microscopic particles. The dispersion then moves from the device surface into the aqueous environment of use.

The device is composed of a core containing a beneficial agent such as a medicament, a polymer which provides gelatinous microscopic particles upon hydration and if desired a hydration modulating agent. The device is completely coated with an insoluble, impermeable coating. The device is completely coated with an insoluble, impermeable coating. The coating contains apertures to expose discrete portions of the surface of the core. The delivery rate of the medicament is a function of the core composition as well as the number and size of the apertures.

In the environment of use, biological fluid contacts the exposed portions of the core surface where hydration of the polymer at the surface begins. As the particles of polymer at the exposed surface absorb water, a gelatinous microscopic dispersion of particles results. Mixed with and dispersed in these microscopic particles are the other components of the core formulation, such as a medicament.

The exposed portion of the core surface is bounded on all sides by the coating. Hydration of the polymer occurs only at the exposed surface of the core, resulting in the steady-state formulation of a gelatinous microscopic particle dispersion within which the drug is dispensed and which moves into the environment of use.

The rate of release of the beneficial agent is not dependent upon the solubility of the beneficial agent in the biological fluid. Rather, the release rate is essentially dependent upon the rate at which the gelatinous microscopic particle dispersion forms at the exposed surface of the device core and exudes from the device carrying with it the beneficial agent and any other core excipient materials that are present.

BACKGROUND OF THE INVENTION

The need for systems that can deliver any drug at a controlled rate of release to an environment of use over a specified period of time is well established.

U.S. Pat. No. 4,814,182 discloses the use of rods or slabs of pre-hydrated and swelled polyethylene oxide hydrogel. The polymer is impregnated with a biologically active agent during the hydration procedure. The hydrated polymer is then dried and partially coated with an impermeable, insoluble material. When placed in an aqueous environment, the polymer swells, but does not dissolve or disintegrate. The entrapped active ingredient is released from the polymer by diffusion. The mechanism of release is based on the ability of the soluble drug to diffuse through the rehydrated hydrogel and move into the aqueous environment.

U.S. Pat. No. 4,839,177 discloses the use of hydrogels compressed to defined geometric forms. In this device, the polymer is mixed with biologically active ingredients to form a core which is affixed to a "support platform" made of an insoluble polymeric material. When hydrated, the swellable, gellable hydrogel expands beyond the device and establishes a superstructure from which the active agent is released either by diffusion, if the active agent is soluble, or by erosion, if the active agent is insoluble. The generation and maintenance of the superstructure is vital to the proper operation of this device.

An osmotic dosage form which utilizes a semipermeable wall containing at least one "exit means" which passes through the wall surrounding a core containing an osmotic agent, a neutral and ionizable hydrogel and an active ingredient is taught in U.S. Pat. No. 4,971,790. The coating of this device is permeable to water from the environment of use. Water moves into the core through the semipermeable membrane. Once inside the device, the water solubilizes the osmotic agent, and hydrates the hydrogels Pressure builds up inside the device, (due to the ionization of the osmogent). Ultimately, the solubilized, ionizable hydrogel, containing the beneficial agent, (the neutral hydrogel) and other core excipients are pumped out of the core, under pressure through an exit means and into the environment of use.

The existing technology is limited since diffusion controlled systems are effective only when soluble active agents are dispensed. For osmotically controlled devices, the technoloy relies upon a wall permeable to the passage of fluid present in the environment of use. Furthermore, these devices require a wall of carefully controlled permeability.

Devices that rely upon the establishment of an extra device superstructure can be altered during in vivo transit, for example, in the gastrointestinal tract. If portions of the superstructure break away, greater surface area is displayed to the environment and unpredictable release of the active agent results.

The usefulness of the above devices would be increased if a device and method were provided to improve the delivery of drugs without regard to their solubility so that diffusion from a swelled polymer or through the superstructure of a polymeric matrix could be avoided. Further utility results from a methodology which provides for a device where the generation of an extra tablet structure could be avoided and the dry ingredients could be contained within a protective coating until release from the device. This would prevent the chance of premature erosion and uncontrolled release of the active agent as well as provide enhanced stability for those active agents that are labile in the fluid of the environment of use.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** is a schematic representation of one embodiment of the instant invention. The device **10**, has a core composition **11**, comprised of a beneficial agent **12**, gel forming polymer **13**, capable of forming a gelatinous microscopic particle dispersion upon hydration. The core may optionally contain a polymer hydration modulating agent **14** and other tablet forming excipients **15**. The core is surrounded by an insoluble, impermeable coating **16**, with a plurality of apertures **17** which expose the core surface to the environment of use.

FIG. **2** is a graph showing the percent of drug released over time from devices of the invention, the devices having a drug:core polymer w/w ratio of 1:3: and 1:1 and wherein the coating polymers are polyvinyl chloride (PVC) or cellulose acetate butyrate (CAB). See Examples 1–4.

FIG. **3** is a graph showing the percent of drug (simvastatin) released over time from a device of the invention wherein the w/w ratio of drug:core polymer is 1:1 and the polymer coating is cellulose acetate butyrate. See Example 5.

FIG. **4** is a graph showing the percent of drug (lovastatin) released from a device of the invention wherein the w:w ratio of drug:core polymer is 1:1 and the polymer coating is cellulose acetate butyrate. See Example 6

FIG. **5** is a graph showing the percent of drug (simvastatin) released from a device of the invention wherein the w:w ratio of drug:core polymer is 40:26.7 and the polymer coating is cellulose acetate butyrate. See Example 7

FIG. **6** is a graph showing the percent of drug (lovastatin) released from a device of the invention wherein the w:w ratio of drug:core polymer is 40:16 and the polymer coating is cellulose acetate butyrate. See Example 8

FIG. **7** is a graph showing the percent of drug (acetaminophen) released from a device of the invention wherein the w:w ratio of drug:core polymer is 2:1 and the polymer coating is cellulose acetate butyrate. See Example 9.

In operation, aqueous solution, from the environment of use, contacts the surface of the core that is exposed within the apertures **17**. The available water begins to hydrate the (microscopic gel bead forming) polymer **13** and gelatinous microscopic particles form at the surface of the core. If present, the polymer hydration modulating agent **14**, at the exposed core surface, is solubilized and establishes the environment required for controlled hydration of the polymer.

As the polymer particles **13** are hydrated, the gelatinous microscopic particles move from the surface. At the same time, the gelatinous microscopic particles move the beneficial agent **12** from the surrounding surface into the environment as well. These particles of beneficial agent move from the core surface into the environment of use in a dispersion with the gelatinous microscopic particles. As a result, controlling the surface area of the core, which is exposed to the environment of use, effectively controls the delivery rate of medicament to the environment.

The instant invention provides a novel device for delivery of an active or beneficial agent (drug), in a dispersion, and produces a beneficial effect which overcomes the disadvantages associated with prior art devices.

The instant invention also provides a device for delivering an active or beneficial agent, in situ as a suspension, at controlled rate over a specified period of time, which delivery is controlled by the selection of components of the device and not the environment surrounding the device.

Further, the instant invention provides a device for controlled delivery of an beneficial agent where the release rate of the beneficial agent is neither related to the solubility of the beneficial agent nor to the in vivo establishment of an extra tablet superstructure.

Additionally, the instant invention provides a device for controlled delivery of an beneficial agent where delivery occurs from the surface of the device not from within a core so that delivery rate is not dependent on diffusion of the active ingredient from inside the device to the environment

Other features and advantages of the invention will be apparent to those skilled in the art from the following detailed description of the invention, taken in conjunction with the drawings and accompanying claims.

DETAILED DESCRIPTION OF THE INVENTION

The novel device of this invention consists essentially of a drug delivery device for the controlled in situ production and release of a dispersion containing a beneficial agent, consisting essentially of:

(A) a compressed core prepared from an admixture comprising

(i) a therapeutically effective amount of a beneficial agent and

(ii) a polymer, which upon hydration forms gelatinous microscopic particles;

(B) a water insoluble, water impermeable polymeric coating, which surrounds and adheres to the core, the coating having a plurality of apertures exposing between about 1 and about 75% of the core surface.

By "drug delivery device" is meant, a dosage form that provides a convenient means of delivering a drug to a subject. The subject can be a human or any other animal. The device is designed to be useful for the delivery of a drug by any pharmaceutically accepted means such as by swallowing, retaining it within the mouth until the beneficial agent has been dispensed, placing it within the buccal cavity, or the like.

By "controlled" production is meant that the rate of release of the beneficial agent, that is the amount of beneficial agent released from the device to the environment of use, follows a predetermined pattern. Thus, relatively constant or predictably varying amounts of the beneficial agent can be dispensed over a specified period of time.

The "gelatinous microscopic particles" are composed of discrete particles of hydrated polymer. Both size and hydration rate of these gelatinous microscopic particles are characteristics of the individual polymers. Illustrative of this type of polymer are sodium polyacrylate, particularly those compositions sold under the trade names "AQUAKEEP® J-550", "AQUAKEEP® J-400", which are trade names for sodium acrylate polymer produced by Seitetsu Kagaku Co., Ltd., Hyogo, Japan. The "AQUAKEEP®" polymers are generically described in U.S. Pat. No. 4,340,706. Also illustrative of this type of polymer are carboxypolymethylenes prepared from acrylic acid crosslinked with allyl ethers of sucrose or pentaerythritol and sold under the trade names "CARBOPOL® 934P" and "CARBOPOL® 974P" which are trade names for two carbomer type polymers produced by B. F. Goodrich Chemical Company, Cleveland, Ohio. These latter polymers are generically described in U.S. Pat. No. 2,909,462 and in the National Formulary XVII at p. 1911, CAS Registry Number 9003-01-4. All of the foregoing references are hereby incorporated by reference.

In the dry state, "CARBOPOL 974P" and "CARBOPOL 934P" particles range in size from 2 to about 7 microns. When these articles are hydrated, gelatinous microscopic particles in the range of 20 microns are produced. When "AQUAKEEP J-550" or "AQUAKEEP J-400" particles are hydrated, the diameter of the gelatinous microscopic particles can range in size from 100 to 1000 microns.

Once the drug delivery device is within the environment of use, the polymer of the compressed core which is exposed to the ambient aqueous solution at the coating apertures, begins to hydrate (the polymer) and produce gelatinous microscopic particles. By "in situ production and release of

a dispersion" is meant that during the production of the gelatinous microscopic particles, soluble and insoluble core components located near the polymer particles become dispersed and mixed in such a manner that a gelatinous dispersion is produced. The dispersion moves from the device into the aqueous solvent, bringing the beneficial agent into the environment of use. In this novel device, the components of the compressed core move into the environment of use, carried along by the gelatinous microscopic particles, continually exposing new surfaces for further hydration and production of the dispersion.

By ("gel") or "gelatinous" is meant a semisolid system consisting of hydrated polymer interpenetrated by the aqueous solvent of the environment of use.

By "exude" is meant to discharge gradually or emit gradually from the apperatures of the device.

By "compressed core" is meant that an admixture of ingredients comprising a beneficial agent, a polymer which produces gelatinous microscopic particles when hydrated, and other ingredients that may affect any of (1) the rate of production of the dispersion; (2) the stability of the components of the dosage form; or (3) the mixing or compression characteristics of the admixture, is blended in such a way to produce a uniform product. This uniform product is then compressed within a die to produce a desired form, normally in the shape of a tablet, capsule or bolus.

The compressed core contains a therapeutically effective amount of beneficial agent and a polymer which upon hydration results in microscopic gel beads. The term "beneficial agent" broadly includes any drug or mixture thereof that can be delivered from the system to produce a beneficial result. The drug can be soluble in the fluid that makes contact with the exposed surface of the core, or it can be essentially insoluble in the fluid.

In the specification and the accompanying claims, the term "drug" and its equivalents includes any physiologically or pharmacologically active substance that produces a localized or systemic effect or effects in animals. The term "animal" includes mammals, humans and primates such as domestic, household, sport or farm animals such as sheep, goats, cattle, horses and pigs, laboratory animals such as mice, rats and guinea pigs, fishes, avians, reptiles and zoo animals.

The active drug that can be delivered by the novel device of this invention, includes inorganic and organic compounds without limitation, including drugs that act on the peripheral nerves, adrenergic receptors, cholinergic receptors, nervous system, skeletal muscles, cardiovascular system, smooth muscles, blood circulatory system, synaptic sites, neuroeffector junctional sites, endocrine and hormone systems, immunological system, reproductive system, skeletal systems, autocoid systems, alimentary and excretory systems, inhibitory and histamine systems, and those materials that act on the central nervous system such as hypnotics and sedatives.

Examples of beneficial drugs are disclosed in *Remington's Pharmaceutical Sciences,* 16th Ed., 1980, published by Mack Publishing Co., Eaton, Pa.; *The Pharmacological Basis of Therapeutics,* by Goodman and Gilman, 6th Ed., 1980, published by the MacMillan Company, London; and *The Merck Index,* 11th Edition, 1989, published by Merck & Co., Rahway, N.J. The dissolved drug can be in various forms, such as charged molecules, charged molecular complexes or ionizable salts. Acceptable salts include, but are not limited to hydrochlorides, hydrobromide, sulfate, laurylate, palmitate, phosphate, nitrate, borate, acetate, maleate, malate, succinate, tromethamine, tartrate, oleate, salicylate, salts of metals, and amines or organic cations, for example quaternary ammonium.

Derivatives of drugs such as esters, ethers and amides without regard to their ionization and solubility characteristics can be used alone or mixed with other drugs. Also, a drug can be used in a form that, upon release from the device, is converted by enzymes, hydrolyzed by body pH or other metabolic processes to the original form, or to a biologically active form.

Specific examples of drugs that may be adapted for use include, Angiotensin-converting enzyme (ACE) inhibitors such as enalapril, lisinapril, and captopril; barbiturates such as pentobarbital sodium, phenobarbital, secobarbital, thiopental and mixtures thereof; heterocyclic hypnotics such as dioxopiperidines and glutarimides; hypnotics and sedatives such as amides and ureas, exemplified by diethylisovaleramide and α-bromo-isovaleryl urea; hypnotic and sedative urethanes and disulfanes; psychic energizers such as isocarboxazid, nialamide, imipramine, amitryptyline hydrochloride, pargylene, and protryptyline hydrochloride; tranquilizers such as chloropromazine, promazine, fluphenzaine, reserpine, deserpidine, and meprobamate; benzodiazepines such as diazepam and chlordiazepoxide; anticonvulsants such as primidone, phenytoin, and ethosuximide; muscle relaxants and antiparkinson agents such as mephenesin, methocarbomal, cyclobenzaprine hydrochloride, trihexylphenidyl hydrochloride, levodopa/carbidopa, and biperiden; antihypertensives such as α-methyldopa and the pivaloyloxyethyl ester of α-methyldopa; calcium channel blockers such as nifedipine, felodipine, diltiazem hydrochloride, diltiazem malate and verapamil hydrochloride; analgesics such as morphine sulfate, codeine sulfate, meperidine, and nalorphine; antipyretics and antiinflammatory agents such as aspirin, indomethacin, ibuprofen, sodium indomethacin trihydrate, salicylamide, naproxen, colchicine, fenoprofen, sulindac, diflunisal, diclofenac, indoprofen and sodium salicylamide; local anesthetics such as procaine, lidocaine, tetracaine and dibucaine; antispasmodics and muscle contractants such as atropine, scopolamine, methscopolamine, oxyphenonium, papaverine; prostaglandins such as PGE_1, PGE_2, $PGF_{2\alpha}$; antimicrobials and antiparasitic agents such as penicillin, tetracycline, oxytetracycline, chlorotetracycline, chloramphenicol, thiabendazole, ivermectin, and sulfonamides; antimalarials such as 4-aminoquinolines, 8-aminoquinolines and pyrimethamine; hormonal and steroidal agents such as dexamethasone, prednisolone, cortisone, cortisol and triamcinolone; androgenic steroids such as methyltestosterone; estrogenic steroids such as 17α-estradiol, α-estradiol, estriol, α-estradiol 3-benzoate, and 17-ethynyl estradiol-3-methyl ether; progestational steroids such as progesterone; sympathomimetic drugs such as epinephrine, phenylpropanolamine hydrochloride, amphetamine, ephedrine and norepinephrine; hypotensive drugs such as hydralazine; cardiovascular drugs such as procainamide hydrochloride, amyl nitrite, nitroglycerin. dipyridamole, sodium nitrate and mannitol nitrate; diuretics such as chlorothiazide, acetazolamide, methazolamide, hydrochlorothiazide, amiloride hydrochloride and flumethiazide, sodium ethacrynate, and furosemide; antiparasitics such as bephenium, hydroxynaphthoate, dichlorophen and dapsone; antineoplastics such as mechlorethamine, uracil mustard, 5-fluorouracil, 6-thioguanine and procarbazine; β-blockers such as pindolol, propranolol, metoprolol, oxprenolol, timolol maleate, atenolol; hypoglycemic drugs such as insulin, isophane insulin; protamine zinc insulin suspension, globin

zinc insulin, extended insulin zinc suspension, tolbutamide, acetohexamide, tolazamide and chlorpropamide; antiulcer drugs such as cimetidine, ranitidine, famotidine and omeprazole; nutritional agents such as ascorbic acid, niacin, nicotinamide, folic acid, choline, biotin, pantothenic acid; essential amino acids; essential fats; ophthalmic drugs such as timolol maleate, pilocarpine nitrate, pilocarpine hydrochloride, atropine sulfate, scopolamine; electrolytes such as calcium gluconate, calcium lactate, potassium chloride, potassium sulfate, sodium fluoride, ferrous lactate, ferrous gluconate, ferrous sulfate, ferrous fumurate and sodium lactate; and drugs that act on α-adrenergic receptors such as clonidine hydrochloride; analgesic drugs such as acetaminophen, oxycodone, hydrocodone, and propoxyphene; antihypercholesterolemic drugs such as simvastatin, pravastatin, lovastatin and genfibrozil; antiinfective drugs such as cefoxitin, cefazolin, cefotaxime, ciprofloxacin, cephalexin, norfloxacin, amprolium, ampicillin, amoxicillin, cefaclor, erythromycin, nitrofurantoin, minocycline, doxycycline, cefadroxil, miconazole, clotrimazole, phenazopyridine, clorsulon, fludalanine, pentizidone, cilastin, phosphonomycin, imipenem; gastrointestinal drugs such as bethanechol, clidinium, dicyclomine, meclizine, prochlorperizine, trimethobenzamide, loperamide, diphenoxylate, and metoclopramide; anticoagulant drugs such as warfarin, phenindione, and anisindione; 5α-reductase inhibitors such as Proscar and other drugs such as trientine, cambendazole, ronidazole, rafoxinide, dactinomycin, asparaginase, nalorphine, rifamycin, carbamezepine, metaraminol bitartrate, allopurinol, probenecid, diethylpropion, dihydrogenated ergot alkaloids, nystatin, pentazocine, phenylpropanolamine, phenylephrine, pseudoephedrine, trimethoprim, and ivermectin.

The above list of drugs is not meant to be exhaustive. Many other drugs will certainly work in the instant invention.

By "therapeutically effective amount" is meant that the quantity of beneficial agent contained in the core, which can be delivered to the environment of use, has been demonstrated to be sufficient to induce the desired effect during studies utilizing the beneficial agent.

Other excipients such as lactose, magnesium stearate, microcrystalline cellulose, starch, stearic acid, calcium phosphate, glycerol monostearate, sucrose; polyvinylpyrrolidone, gelatin, methylcellulose, sodium carboxymethylcellulose, sorbitol, mannitol, polyethylene glycol and other ingredients commonly utilized as stabilizing agents or to aid in the production of tablets may also be present in the core.

The drug can be in the core as a dispersion, particle, granule, or powder. Also, the drug can be mixed with a binder, dispersant, emulsifier or wetting agent and dyes.

The active agent may comprise from 0.01% to 75% of the core weight. Generally, the device can house from 0.05 ng to 50 grams of active agent or more, with individual devices containing, for example, 25 ng, about 1 mg, about 5 mg, about 250 mg, about 500 mg, about 1.5 g, or the like.

The "polymer which upon hydration forms gelatinous microscopic particles" useful in the novel device of this invention broadly encompasses any polymer that, upon hydration, is capable of producing discrete gelatinous microscopic particles which support a dispersion, including the beneficial agent, as it forms. The gel forming polymer used also must exude from the core surface in such a way that the beneficial agent is carried into the environment of use. Upon hydration, the gelatinous microscopic particles must be predisposed to leave the surface taking the drug with it. This assures a constant surface area exposed to the solvent of the environment of use and maintains the appropriate rate of release.

Polymers that form usable gelatinous microscopic particles, include the superabsorbant polymers such as "AQUAKEEP J550", "AQUAKEEP J400", "CARBOPOL 974P" and "CARBOPOL 934P" and their pharmaceutically acceptable salts. By "pharmaceutically acceptable salts" of the polymers is meant the acid form of the polymer neutralized by converting all or a portion of the free acid functional groups to their salt form. The core of the device contains from 5% to 75% by weight of the dry microscopic particle polymer.

The "polymer hydration modulator" useful in the novel device of this invention broadly encompasses any water soluble compound that can inhibit or enhance the rate of hydration of the gel forming polymer of the core. Among the groups of compounds that can exert this effect are acids, bases, and the salts of acids and bases such as adipic acid, citric acid, fumaric acid, tartaric acid, succinic acid, sodium carbonate, sodium bicarbonate, betaine hydrochloride, sodium citrate, arginine, meglamine, sodium acetate, sodium phosphates, potassium phosphates, calcium phosphate, ammonium phosphate, magnesium oxide, magnesium hydroxide, sodium tartrate and tromethamine. Other compounds that can be used as polymer hydration modifiers include sugars such as lactose, sucrose, mannitol, sorbitol, pentaerythritol, glucose and dextrose. Polymers such as microcrystalline cellulose and polyethylene glycol as well as surfactants and other organic and inorganic salt can also be used to modulate polymer hydration.

The hydration modulating agents are solubilized by the aqueous media of the environment and establish an environment such that the pH, ionic strength or hydrophilic character is appropriate for the desired polymer microscopic gel bead hydration rate. For example, these hydration modulating agents can enhance or retard the neutralization of acidic functional groups on the polymer which affects the rate of hydration.

The core compartment containing the drug, hydration modulator, and microscopic particle polymer as described herein, is typically in the form of a solid conventional tablet. Generally, the core is compressed into its final shape using a standard tablet compressing machine. The core may contain compressing aids and diluents such as lactose that assist in the production of compressed tablets. The core can be comprised of a mixture of agents combined to give the desired manufacturing and delivery characteristics. The number of agents that may be combined to make the core is substantially without an upper limit with the lower limit equaling two components: the gel forming polymer and the beneficial agent.

The preferred specifications for the core are summarized below and include:

1. Core Drug Loading (size): about 0.01% to about 75% by weight of the total core mass or about 0.05 nanogram to about 50 grams or more (includes dosage forms for humans and animals).

2. Polymer Hydration. Modulator: 0% to about 75% by weight of the total core mass.

3. Gel Forming Polymer: about 5 to about 75% by weight of the total core mass.

In cases where the drug, the gel forming polymer and polymer hydration modulating agent exhibit the desired release rate, stability, and manufacturing characteristics, there is no critical upper or lower limit as to the amount of

drug that can be incorporated into a core mass. The ratio of drug to excipient is dictated by the desired time span and profile of release, and the pharmacological activity of the drug.

Generally the core will contain 1% to 50% by weight of an beneficial agent admixed with other solute(s). Representative of compositions of matter that can be released from the device and can function as a solute are, without limitation, those compositions as described.

The coating, applied to the core of the invention, is a material that is impermeable and insoluble in the fluid of the environment of use, can form films, and does not adversely affect the drug, animal body, or host. The coating is impermeable to water and also impermeable to the selected product, drugs, polymer hydration modulating agents, or to other compounds in the device. This impermeable material is insoluble in body fluids and non-erodible or it can be bioerodible after a predetermined period with bioerosion following the end of the active drug release period. In each instance, it is impermeable to solvent and solute(s) and is suitable for construction of the device.

By "impermeable" is meant that the influx of water across the coating is de minimus. Flux of water into the device is via the apertures placed in the coating.

The polymeric coating is applied to and adheres to the entire surface of the core. Apertures are produced in the coating to expose the core, using either a drill, a coring device or any other pharmaceutically accepted means.

The apertures allow liquids from the environment of use to make contact only with exposed portions of the core when in use. The number, size and configuration of the apertures is chosen to provide the release rate required to suit a pharmacologically recognized requirement since the gel dispersion can form only where the apertures allow such core-liquid contact.

The coating can be applied by dipping the cores into a suitable solution of the polymer or by coating the cores with a pharma-acceptable polymer coating process. Among the groups of polymers that can provide this type of protection are cellulose acetate, cellulose acetate butyrate, ethylcellulose, polyvinylacetate, polyvinyl chloride and polymers of acrylic and methacrylic acid esters. In addition, other materials may be included with the coating to enhance its stability, color, elasticity, ease of application or opacity. These include plasticizers such as dibutylsebacate, diethylphthalate, triethylcitrate and polyethylene glycol.

The coating is applied to a thickness of from 1 to 1000 microns but preferably 10 to 500 microns typically, although thinner and thicker coatings fall within the scope of the invention.

The expression "aperture" as used herein, refers to ports through the coating which expose the surface of the core to the environment. The size and number of apertures is chosen to effect the desired release rate. Exposure of from about 1% to about 75% of the core surface is contemplated by this invention.

The apertures are generally positioned in a regular pattern on both faces of the device although they can be positioned anywhere on the core including the edges or all on one face.

The apertures are generally circular but may be of any design that results in the proper release rate. When the aperture is circular, its diameter ranges from about 0.1 mm to about 20 mm with diameters of about 0.2 to 3.5 mm typical. The number of apertures in each device may range from about 2 to about 1000 or more. Typically, the number of apertures in each dosage form ranges from about 5 to about 100.

The apertures may be made by drilling the appropriate size hole through the coating using a mechanical or laser-based process. In the preferred embodiment, a digital laser marking system is used to drill the holes required. This system allows for an array of apertures to be drilled on both faces of a dosage form simultaneously and at rates suitable for production of dosage forms.

The process utilizes a digital laser marking system (for example the DigiMark® variable marking system, available from Directed Energy, Inc.) to produce an unlimited number of holes through the surface or coating of the dosage form, at rates practically suitable for production of dosage forms.

The steps involved in this laser drilling process are as follows: a digital laser marking system is focused at a laser stage; the dosage form is moved onto the laser stage of the digital laser marking system is pulsed to energize those laser tubes needed to drill the desired apertures along a linear array on the dosage form, the dosage form is moved forward on the laser stage and the digital laser marking system is again pulsed as needed to produce an additional linear array of apertures; the dosage form is then removed from the laser stage.

Additional, preferred specifications for the impermeable wall include: a mixture of eight parts by weight of cellulose acetate butyrate, two parts by weight of cellulose acetate and one part by weight of diethylphthalate. This mixture is dissolved in a solution of methylene chloride and methanol (about 3:1 v/v) and sprayed onto the cores to a thickness of about 250 microns. Another preferred coating consists of five parts by weight of cellulose acetate butyrate and one part by weight of triethyl citrate dissolved in a mixture of acetone and methanol (about 3:1 v/v). This mixture is sprayed on the core or dipped into the mixture so that a coating of 100 microns is applied.

The polymers used in the coating which are herein described are known to the art or can be prepared according to the procedures in *Encyclopedia of Polymer Science and Technology,* Vol. 3, published by Interscience Publishers, Inc., New York, in *Handbook of Common Polymers* by Scott, J. R. and Roff, W. J., 1971, published by CRC Press, Cleveland, Ohio.

The following examples illustrate the preparation of the drug delivery device of this invention and their controlled release of one or more therapeutically active ingredients into an environment of use and as such are not to be considered as limiting the invention set forth in the claims appended hereto.

EXAMPLES

In the following examples, the hydroxymethylglutaryl-coenzyme A reductase inhibitors (HMG CoA reductase inhibitors) simvastatin and lovastatin are used as model drugs. These drugs are highly effective in the reduction of serum cholesterol levels in humans and possess neither acidic nor basic functionality. The aqueous solubilities of simvastatin and lovastatin are 0.03 mg/ml and 0.00044 mg/ml respectively, at 20° C. The generation of a dispersion, in situ, from the components of a solid core is disclosed. The anti-arthritic, indomethacin and the analgesic, acetaminophen serve as examples of beneficial agents which are deliverable with this device. This permits the successful formulation of poorly aqueous soluble (simvastatin, lovastatin, indomethacin), moderately soluble (acetominophren) and freely water soluble drugs into a delivery device.

Example 1

Tablets for the controlled release of the drug indomethacin were made as follows, utilizing a 1:1 weight ratio of drug: J-550 polymer.

Core Component	Weight (g)
"AQUAKEEP J-550"	2
Indomethacin	2
Avicel PH 101	400 mg
Povidone (K29-32)	60 mg in 6 ml EtOH

Indomethacin, J-550 and Avicel were mixed thoroughly and granulated with the polyvinylpyrrolidone as a 1% by weight solution in ethyl alcohol. The solvated mass was passed through a sieve of standard mesh size 18 then dried overnight at 45° C. Tablet cores were prepared from the resulting granulation by taking approximately 115 mg of the granules and compressing them on a Carver® press using ¼" standard concave punches.

The tablet cores prepared as above were coated with polyvinyl chloride (PVC) coating by dip coating 5 times in diluted clear polyvinyl chloride cement. These tablets were rolled on edge each time on a teflon sheet to prevent sticking. Each tablet was allowed to dry approximately one hour between subsequent coatings and the tablets were dried for approximately 8 hours after the fifth coat was applied. Five 1.5 mm diameter circular openings were drilled through the coating on each face of the tablets.

The release of indomethacin from the coated, drilled tablets into 900 ml of pH 7.5 phosphate buffer at 37° C. with 100 rpm stirring was then determined (USP Apparatus 2). The absorbance of indomethacin was measured at 320 nm using a Cary-14 spectrophotometer. Indomethacin release profiles for the coated, drilled dosage forms are shown in FIG. **2**.

Example 2

Tablets were prepared according to the procedure of Example 1, except that the core mixture comprised indomethacin and J-550 polymer in the weight ratio of 1:3. Indomethacin release rates were determined as in Example 1 and are shown in FIG. **2**.

Examples 3 and 4

Tablets were prepared according to the procedures of Examples 1 and 2. Core compositions of indomethacin and J-550 in a weight ratio of 1:1 and 1:3 were spray coated with cellulose acetate butyrate CAB 381-20 (Eastman Fine Chemicals) in a Freund® Model HCT-Mini Hi-Coater (8-inch pan) from a methylene chloride:methanol (1:1) solution at 4% by weight solids. Coating thicknesses were 250 microns for the 1:1 indomethacin:J-550 core composition and 400 microns for the 1:3 core composition. The indomethacin release rates were determined as in Example 1 and are shown in FIG. **2**.

Example 5

Tablets for the controlled release of simvastatin were prepared from the following formulation:

Ingredient	mg/Tablet
Simvastatin	100
"AQUAKEEP J-550"	100
Avicel PH101	100
Povidone (K29-32)	7.8
Magnesium Stearate	1.5
Total	309.3

The dry ingredients with the exception of magnesium stearate were thoroughly mixed and granulated with absolute alcohol. The solvated mass was passed through a No. 18 stainless steel sieve and then dried for twenty-four hours at 37° C. The dried granules were forced through a No. 35 mesh stainless steel sieve before lubricating with magnesium stearate. This homogeneous mixture was compressed into tablets using ⅜ inch standard concave round punches. The tablets were compressed to a hardness of 19 kg. The tablets were coated in a Freund® Model HCT-Mini Hi-Coater (8-inch pan) to a thickness of 250 microns using the following coating formulation:

Ingredient	Amount
Cellulose Acetate Butyrate CAB 381-20	48 g
Cellulose Acetate CA 435-75S	12 g
Methylene Chloride	2250 ml
Methanol	750 ml
Diethylphthalate	6 g

Circular openings in the coating were made using a tubular boring tool with an i.d. of 2.80 mm which provided openings of nearly 3.0 mm. The in vitro release of simvastatin from tablets with three circular openings of 3.0 mm diameter on each face was carried out at 37° C. using USP Apparatus 2 into pH 7.4 phosphate buffer with 0.5% by weight weight sodium dodecyl sulfate at 100 rpm. The results are shown in FIG. **3**.

Example 6

Tablets for the controlled release of lovastatin were prepared from the following formulation:

Ingredient	mg/Tablet
Lovastatin	20
"CARBOPOL 974P"	13.4
Sodium Citrate Dihydrate	13.3
Lactose Hydrous (spray dried)	13.3
Povidone (K29-32)	3.0
Total	63.0

The ingredients were combined and thoroughly mixed in a mortar and pestle, then granulated with 90% alcohol: 10% by volume water. This wet mass was passed through a No. 20 stainless steel sieve and dried overnight at 40° C. The resulting mixture was compressed into tablets using ¼ inch standard concave punches. The tablets were compressed to a thickness of 2.33 mm and a hardness of 9 kg.

The tablets were coated to a thickness of 250 microns with the following formulation using a Freund® Model HCT-Mini H-Coater (8-inch pan).

Ingredient	Amount
Cellulose Acetate Butyrate CAB 381-20	64 g
Cellulose Acetate CA 435-755	16 g
Methylene Chloride	3000 ml
Methanol	1000 ml
Diethylphthalate	8 g

In vitro release tests were carried out at 37° C. using USP Apparatus 2 into pH 7.4 phosphate buffer containing 0.2% sodium dodecyl sulfate at 50 rpm. The drug released was monitored by flow-through UV spectrophotometry. The drug released from coated tablets with 1.75 mm diameter circular openings bored through the coating on each face is shown in FIG. **4**.

Example 7

Simvastatin tablets were prepared from the following formulation:

Ingredients	mg/Tablet
Simvastatin	40
CARBOPOL® 974P	26.7
Sodium Citrate Dihydrate (milled to 100–200 mesh)	26.7
Lactose Hydrous NF (spray dried)	26.6
Povidone USP (K29-32)	6.0
Butylated Hydroxyanisole NF	0.04
Magnesium Stearate NF	0.6
Total	126.64

The simvastatin, CARBOPOL®, milled sodium citrate, lactose and polyvinyl-pyrrolidone were combined, mixed thoroughly and granulated with 10% by weight water in alcohol containing the required BHA. The wet mass was forced through a No. 18 sieve and dried overnight. The dry granulation was lubricated with magnesium stearate and the homogenous mixture compressed using ¼ inch standard concave round tooling and a compression force of 1000 lbs. The compressed tablets had a thickness of 3.89 mm and a hardness of 10 kg. The tablets were spray coated to a coat thickness of 100 microns in a Freund® HCT-Mini Hi-Coater (8-inch pan) using the following coating formulation:

Ingredient	Amount
Cellulose Acetate Butyrate CAB 381-20	80 g
Triethyl Citrate	16 g
Acetone	3000 ml
Methanol	1000 ml

In vitro release tests were carried out at 37° C. using USP Apparatus 2 into pH 7.4 phosphate buffer containing 0.4% by weight sodium dodecyl sulfate at 50 rpm. The drug released was monitored by flow-through UV spectrophotometry. The results for tablets with one 2.8 mm diameter circular opening per tablet face are shown in FIG. **5**.

Example 8

Tablets for the controlled release of lovastatin were prepared from the following formulation:

Ingredient	mg/Tablet
Lovastatin	40
CARBOPOL 974P NF	16
Sodium Citrate USP (dihydrate)	32
Lactose Hydrous NF (spray dried)	16
Povidone USP (K29-32)	5.2
Butylated Hydroxyanisole NF	0.04
Magnesium Stearate NF	0.55
Total	109.79

The granular sodium citrate dihydrate was reduced in particle size such that 90% by weight went through a No. 120 mesh sieve. The milled sodium citrate dihydrate was combined with lovastatin, CARBOPOL®, lactose and polyvinylpyrrolidone, mixed thoroughly then granulated using Alcohol USP. The solvated mass was passed through a #10 screen then dried overnight at 50° C. The dried granulation was milled, then lubricated with magnesium stearate. The homogeneous mixture was compressed into tablets using ¼ inch standard concave tooling. The tablets were compressed to a thickness of 3.43 mm and a hardness of 10.5 kg. The tablets were coated to a thickness of 100 microns with the following coating formulation using a Glatt WSG-3 fluidized bed column spray coater.

Ingredients	Amount
Cellulose Acetate Butyrate (CAB 381-20)	80 g
Triethyl Citrate NF	16 g
Acetone NF	3000 ml
Alcohol USP	1000 ml

In vitro release tests were carried out as in Example 7 for tablets with bored circular openings of 1.5 mm diameter and three per tablet face. The results are shown in FIG. **6**.

Example 9

Tablets for the controlled release of acetaminophen were prepared according to the following formulation:

Ingredient	mg/Tablet
Acetaminophen	20
CARBOPOL® 974P	10
Sodium Citrate Dihydrate	20
Lactose Hydrous (spray dried)	10
Povidone (K29-32)	3
Total	63

The ingredients above were combined, mixed thoroughly then granulated with alcohol. The solvated mass was passed through a No. 20 mesh sieve and dried overnight at 40° C. The dried granulation was compressed into tablets using ¼ inch standard concave tooling. The tablets were compressed to a thickness of 2.31 mm and a hardness of 6–7 kg. The tablets were coated as in Example 6.

In vitro release tests were carried out at 37° C. using USP Apparatus 2 into pH 7.4 phosphate buffer at 50 rpm. The drug released was monitored by flow-through UV spectrophotometry. The results for tablets with one 2.75 mm diameter circular opening per tablet are shown in FIG. **7**.

Example 10

Tablets cores containing lovastatin, CARBOPOL® 974P, trisodium citrate and lactose in relations of 5:2:4:2 were prepared using the procedure described in Example 8.

Varying numbers of apertures were mechanically drilled in each face of the coated tablets. The diameter of the apertures ranged from about 0.23 mm to about 3 mm in diameter as measured by microscopic imaging using an Analytical Imaging Concepts IM4000. In vitro release tests wre carried out at 37° C. using USP Apparatus 2 in pH 7.4 phosphate buffer containing 0.4% sodium dodecyl sulfate at 50 rpm. The drug released was monitored by flow-through UV spectrophotometry.

The results of the study are shown in Table I.

Example 11

Twenty-four (24) apertures of 0.35 mm in diameter were drilled in each face of the coated tablets prepared for the study in Example 10 using the DIGIMARK™ digital laser marking system. The apertures were measured by microscopic imaging using an Analytical Imaging Concepts IM4000. Release rates were studied as in Example 10. The results are shown in Table II.

TABLE I

Number of holes	Initial Drug Release Rate (mg/h) (mg/h)	Hole Diameter (m/m)	Hole Surface Area (m/m^2)	Release Rate/Hole Surface Area (mm/h)/mm^2
5	0.4	0.23	0.42	1.06
10	0.91	0.23	0.83	1.10
20	2.14	0.23	1.66	1.29
40	3.57	0.23	3.32	1.07
1	0.35	0.53	0.44	0.79
3	1.03	0.53	1.32	0.78
5	1.92	0.53	2.21	0.87
10	3.36	0.53	4.41	0.76
5	4.28	1.07	8.99	0.48
7	5.80	1.07	12.59	0.46
1	1.96	1.6	4.02	0.49
2	3.55	1.6	8.04	0.44
3	5.07	1.6	12.06	0.42
1	2.22	2.0	6.28	0.35
1	2.73	2.4	9.05	0.30
1	4.17	3.0	14.14	0.29

TABLE II

Number of holes	Initial Drug Release Rate (mg/h)	Hole Surface Area (m/m^2)	Release Rate/Hole Surface Area (mg/h)/mm^2
24	3.96	4.62	0.86

Example 12

Tablets for the controlled release of nifedipine were prepared from the following formulation:

Ingredient	mg/Tablet
Nifedipine micronized	69
CARBOPOL 974P NF	30
Dibasic Sodium Phosphate (anhydrous) USP	75
Lactose Hydrous NF (spray dried)	15
Povidone USP K-90	5
Magnesium Stearate NF	0.88
Total	194.88

The nifedipine was milled using the Model 00 Jet-O-Mizer to a 10 micron median particle size. The micronized nifedipine was combined with dibasic sodium phosphate, carbopol, lactose and polyvinylpyrrolidone, mixed thoroughly then granulated using an aqueous alcoholic solvent blend (10% by volume water). The solvated mass was passed through a #20 screen then dried initially at 60° C. for two to four hours, then at 40° C. overnight. Magnesium stearate was sifted over the dried granulation and the total mixture passed through a #40 screen. The homogenous mixture was compressed into tablets using 5/16 inch standard concave tooling. The tablets were compressed to a thickness of 3.6 mm and a hardness of 20 kg. The tablets were coated to a thickness of 100 microns with the following coating formulation using a UniGlatt fluidized bed column spray coater.

Ingredient	Amount
Cellulose Acetate Butyrate (Eastman 381-20)	140 g
Triethyl Citrate NF	14 g
Methylene Chloride	3000 ml
Alcohol USP	1000 ml

The tablets were mechanically drilled with 18–0.45 mm diameter opening through the coating on each face then overcoated to a thickness of approximately 150 microns with the following coating formulation using a UniGlatt fluidized bed column spray coater.

Ingredient	Amount
Hydroxypropyl Methylcellulose (Methocel E5)	100 g
Ethylcellulose (Ethocel E10)	25 g
Water	100 ml
Alcohol	1000 ml
Methylene Chloride	2500 ml

In vitro release tests were carried out at 37° C. using USP Apparatus 2 into pH 7.4 phosphate buffer containing 2% sodium dodecyl sulfate at 100 rpm. The drug released was monitored by flow-through UV spectrophotometry at 340 nm.

What is claimed is:

1. A drug delivery device for the controlled in situ production and release of a dispersion containing simvastatin, which is:

(A) a compressed core prepared from an admixture comprising:

(i) a therapeutically effective amount of simvastatin; and

(ii) a polymer which upon hydration forms gelatinous microscopic particles, wherein the polymer is selected from the group consisting of sodium polyacrylate, carboxypolymethylenes, and the pharmaceutically acceptable salts thereof, and wherein the carboxypolymethylenes are prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol; and

(B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, wherein the polymer is selected from the group consisting of cellulose acetate, cellulose acetate butyrate, ethylcellulose, polyvinylacetate, polyvinyl chloride, polymers of acrylic and methacrylic acid esters, and combinations of these polymers, and the plasticizer is selected from the group consisting of dibutylsebacate, diethylphthalate, triethylcitrate and polyethylene

glycol, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;

and wherein the release rate of the beneficial agent from the device is a function of the number and size of the apertures.

2. The device of claim **1** wherein the amount of simvastatin in the core comprises from 0.01% to 75% by weight of the core mixture.

3. The device of claim **1** wherein the amount of polymer which upon hydration produces gelatinous microscopic particles in dry form comprises from about 5% to about 75% by weight of the core mixture.

4. The device of claim **1** wherein the water insoluble, water impermeable polymeric coating is comprised of a polymer selected from the group consisting of polyvinyl chloride, cellulose acetate, cellulose acetate butyrate, ethylcellulose and combinations of these polymers; and a plasticizer selected from the group consisting of diethylphthalate, dibutylsebacate and triethylcitrate.

5. The device of claim **1** wherein the polymer in the water insoluble, water impermeable polymeric coating is cellulose acetate butyrate.

6. The device of claim **1** wherein the plasticizer in the water insoluble, water impermeable polymeric coating is triethylcitrate.

7. The device of claim **1** wherein the polymer which upon hydration forms gelatinous microscopic particles is selected from the group consisting of carboxypolymethylenes prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol, and the pharmaceutically acceptable salts thereof.

8. The device of claim **1** wherein the compressed core further comprises at least one polymer hydration modulating agent selected from the group consisting of acids, bases, salts, sugars, surfactants, and soluble polymers.

9. The device of claim **8** wherein the polymer hydration modulating agent or agents are selected from the group consisting of sodium phosphates and microcrystalline cellulose.

10. The device of claim **1** wherein the compressed core is further comprised of one or more compressing aids and diluents.

11. The device of claim **1** wherein the compressed core is further comprised of lactose.

12. The device of claim **1** wherein the apertures in the coating range from 0.1 mm to 20 mm at their widest point.

13. The device of claim **1** wherein the number of apertures ranges from 2 to 1000.

14. The device of claim **13** wherein the number of apertures ranges from 5 to 100.

15. The device of claim **1** wherein the apertures are positioned in a regular pattern on both faces of the device.

16. The device of claim **1** further comprised of at least one material for enhancing at least one of the characteristics of the water impermeable polymeric coating, wherein the characteristics are selected from the group consisting of stability, color, elasticity, ease of application, and opacity.

17. The device of claim **16** comprised of at least one material for enhancing the elasticity of the water impermeable polymeric coating.

18. The device of claim **16** comprised of at least one material for enhancing the opacity of the water impermeable polymeric coating.

19. The device of claim **16** comprised of at least one material for enhancing the ease of application of the water impermeable polymeric coating.

20. A drug delivery device for the controlled in situ production and release of a dispersion containing simvastatin, which is:

(A) a compressed core prepared from an admixture comprising:

(i) from 0.01% to 75% by weight of the core mixture of a therapeutically effective amount of simvastatin; and

(ii) from about 5% to about 75% by weight of the core mixture of a polymer which upon hydration forms gelatinous microscopic particles, wherein the polymer is selected from the group consisting of sodium polyacrylate, carboxypolymethylenes and the pharmaceutically acceptable salts thereof, and wherein the carboxypolymethylenes are prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol; and

(B) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, wherein the polymer is selected from the group consisting of polyvinyl chloride, cellulose acetate, cellulose acetate butyrate, ethylcellulose and combinations of these polymers, and the plasticizer is selected from the group consisting of diethylphthalate, dibutylsebacate and triethylcitrate, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface;

and wherein the release rate of drug from the device is a function of the number and size of the apertures.

21. The device of claim **20** wherein:

the polymer which upon hydration forms gelatinous microscopic particles is selected from the group consisting of carboxypolymethylenes prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol and the pharmaceutically acceptable salts thereof;

the polymer in the water insoluble, water impermeable polymeric coating is cellulose acetate butyrate; and

the plasticizer in the water insoluble, water impermeable polymeric coating is triethylcitrate.

22. The device of claim **21** wherein the compressed core is further comprised of at least one polymer hydration modulating agent selected from the group consisting of sodium phosphates and microcrystalline cellulose.

23. A process for the preparation of a drug delivery device for the controlled in situ production and release of a dispersion containing a beneficial agent characterized by having a compressed core surrounded by a water insoluble, water impermeable polymeric coating, comprising the steps of:

(A) preparing a uniform mixture by either dry mixing or wet granulating a polymer which upon hydration produces gelatinous microscopic particles, the beneficial agent and other excipients used in the preparation of the core, wherein the polymer is selected from the group consisting of sodium polyacrylate, carboxypolymethylenes, and the pharmaceutically acceptable salts thereof, and wherein the carboxypolymethylenes are prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol;

(B) compressing the uniform mixture into cores;

(C) coating the entire core with the water insoluble, water impermeable polymeric coating comprised of a polymer and a plasticizer, wherein the polymer is selected from the group consisting of cellulose acetate, cellulose acetate butyrate, ethylcellulose, polyvinylacetate, polyvinyl chloride, polymers of acrylic and methacrylic acid esters, and combinations of these polymers, and the plasticizer is selected from the group consisting of

dibutylsebacate, diethylphthalate, triethylcitrate and polyethylene glycol; and

(D) forming apertures through the coating.

24. The process of claim **23** wherein the beneficial agent is simvastatin.

25. The process of claim **23** wherein the uniform mixture of step (A) is prepared by either dry mixing or wet granulating a polymer hydration modulating agent with the polymer, the beneficial agent and the other excipients.

26. The process of claim **25** wherein at least one material for enhancing at least one of the characteristics of the water impermeable coating is added either before or after, or before and after, application of the water impermeable polymeric coating, wherein the characteristics are selected from the group consisting of stability, color, elasticity, ease of application, and opacity.

27. The process of claim **26** wherein the beneficial agent is simvastatin.

28. A drug delivery device for the controlled in situ production and release of a dispersion containing simvastatin, which is:

(A) a compressed core prepared from an admixture comprising:

(i) a therapeutically effective amount of simvastatin; and

(ii) a polymer which upon hydration forms gelatinous microscopic particles, wherein the polymer is selected from the group consisting of sodium polyacrylate, carboxypolymethylenes, and the pharmaceutically acceptable salts thereof, and wherein the carboxypolymethylenes are prepared from acrylic acid crosslinked with allylethers of sucrose or pentaerythritol; and

(B) a water insoluble polymeric coating comprising a polymer and a plasticizer, which surrounds and adheres to the core, wherein the polymer is selected from the group consisting of polyvinyl chloride, cellulose acetate, cellulose acetate butyrate, ethylcellulose and combinations of these polymers, and the plasticizer is selected from the group consisting of diethylphthalate, dibutylsebacate, and triethylcitrate, the coating having a plurality of formed apertures exposing between about 1 and about 75% of the core surface; and wherein the release rate of the beneficial agent from the device is a function of the number and size of the apertures.

* * * * *

US006245357B1

(12) **United States Patent**
Edgren et al.

(10) **Patent No.: US 6,245,357 B1**
(45) **Date of Patent: Jun. 12, 2001**

(54) **EXTENDED RELEASE DOSAGE FORM**

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(73) Assignee: **Alza Corporation**, Mountain View, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/249,700**

(22) Filed: **Feb. 12, 1999**

Related U.S. Application Data

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(51) **Int. Cl.**[7] **A61K 9/24**; A61K 9/22

(52) **U.S. Cl.** **424/473**; 424/468

(58) **Field of Search** 424/473, 472, 424/443, 465, 489; 604/892; 514/289

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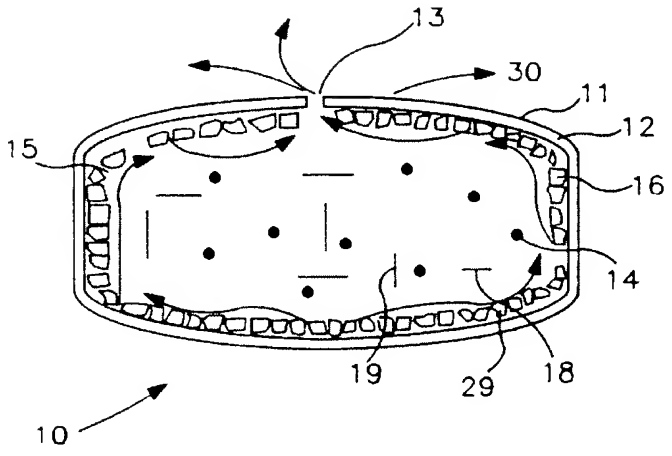
Assistant Examiner—Blessing Fubara
(74) *Attorney, Agent, or Firm*—John A. Dhuey; Steven F. Stone

(57) **ABSTRACT**

A dosage form comprising a composition comprising a drug surrounded by an interior and an exterior wall with an exit for administering the drug to a patient; and a method of using the dosage form are disclosed for an indicated therapy.

66 Claims, 4 Drawing Sheets



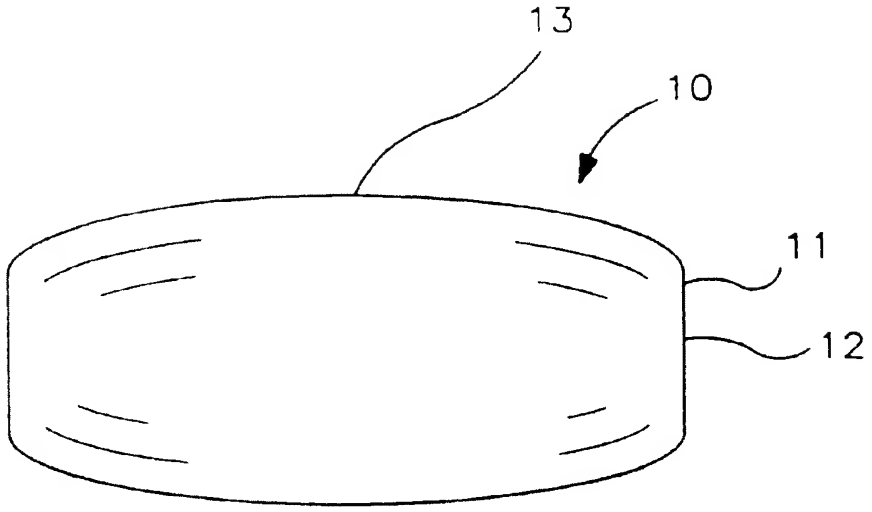


FIG. 1

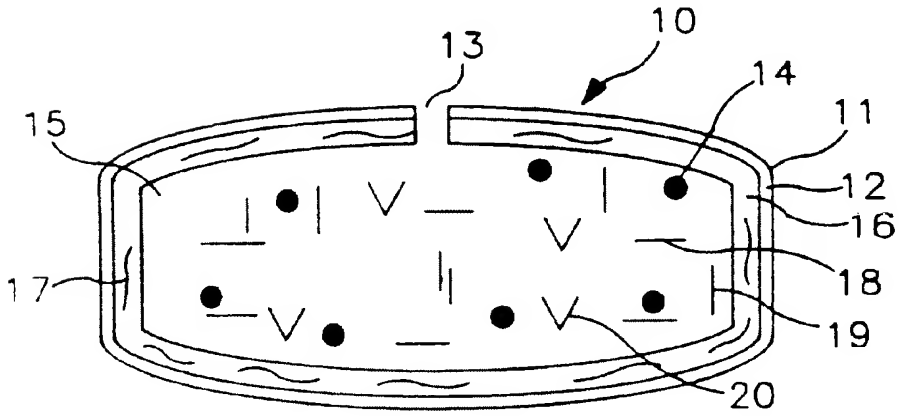


FIG. 2

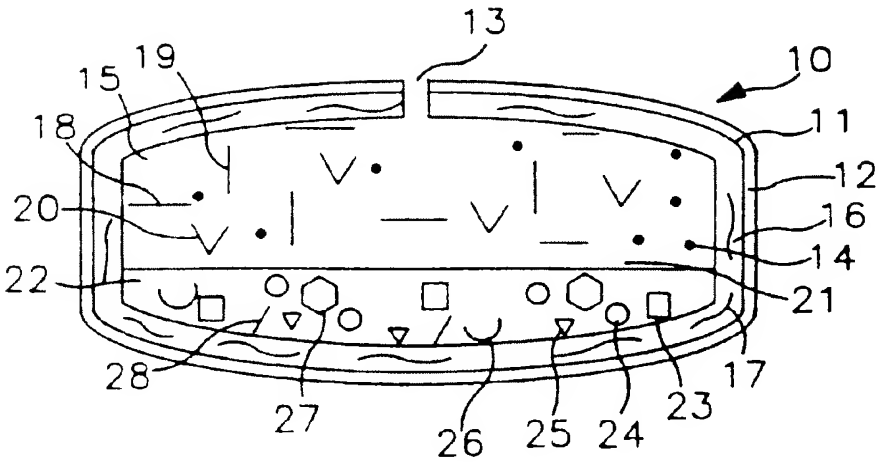

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FIG. 3

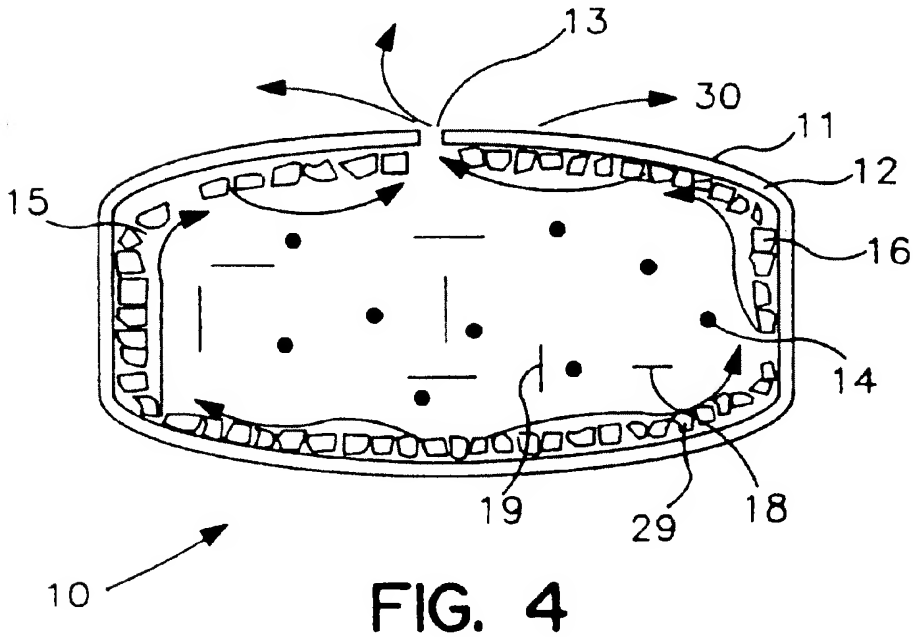
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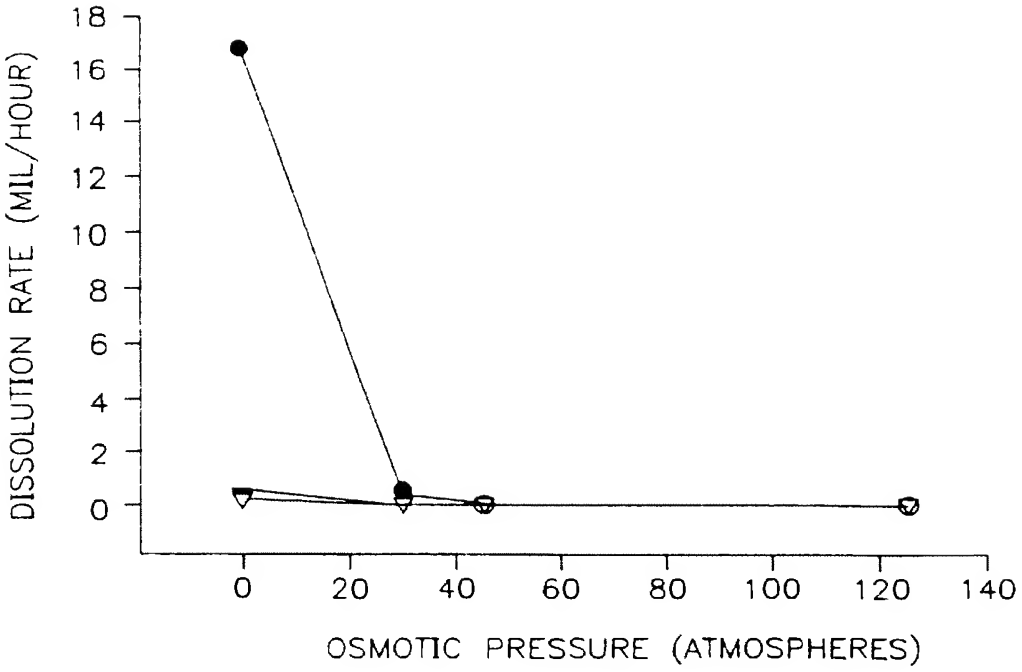
FIG. 4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OSMOTIC PRESSURE (ATMOSPHERES)

FIG. 5

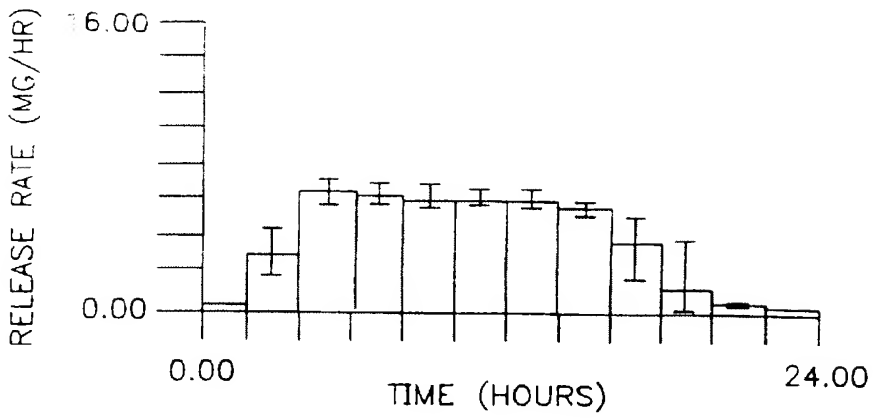

FIG. 6

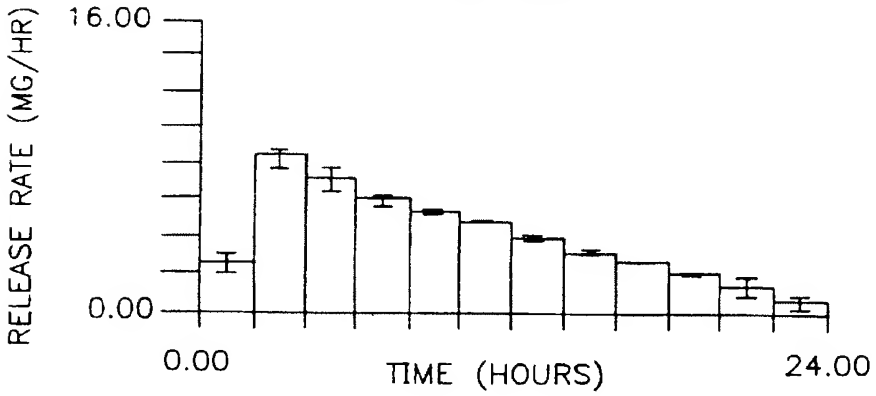

FIG. 7

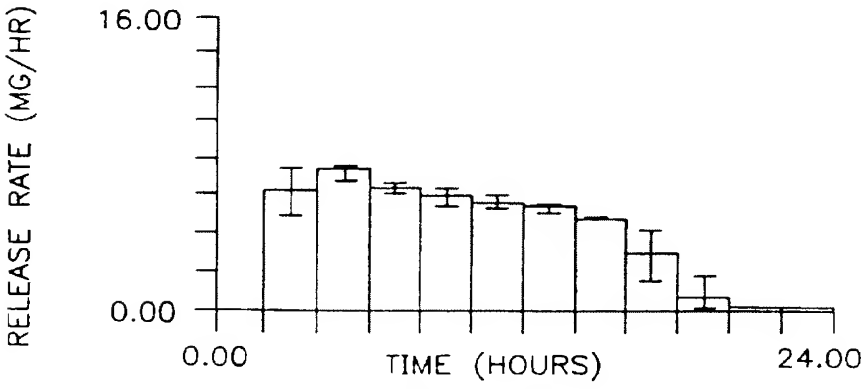

FIG. 8

EXTENDED RELEASE DOSAGE FORM

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefits of provisional application U.S. Ser. No. 60,077,133, filed Mar. 6, 1998 under 35 U.S.C §119(e).

FIELD OF THE INVENTION

This invention pertains to both a novel and therapeutically useful dosage form. The invention, more particularly, relates to a dosage form that administers a dose of drug in an extended and linear-release profile for an indicated therapy. Specifically, the invention concerns a dosage form comprising a drug formulation enveloped by two walls with the formulation and walls acting in concert to provide the extended, linear-nondeclining-release drug delivery profile. The invention concerns also a method of administering the dosage form to provide a dose of drug for therapy.

BACKGROUND OF THE INVENTION

To improve the effectiveness of drug therapy and to reduce possible systematic side effects, many attempts have been made to deliver drugs in a controlled profile to human patients. The advantage of controlled release dosage forms are well-known in both the pharmaceutical and medical sciences. The therapeutical benefits of controlled-release dosage forms include the pharmacokinetic ability to maintain a preplanned blood level of an administered drug over a comparatively longer period of time. The therapeutical benefits include also a simultaneous increase in patient compliance and a reduction in the number of doses of drug administered to a patient.

The prior art made available controlled release dosage that sought to provide a drug release rate profile that matched the blood physiological and chronopharmacological requirements needed for therapy. For example, an osmotic dosage form for delivering various drugs to a patient environment of use is presented in U.S. Pat. No. 3,845,770 issued to patentees Theeuwes and Higuchi, and in U.S. Pat. No. 3,916,899 issued to the same patentees. The dosage forms disclosed in these patents are manufactured comprising a wall that surrounds a compartment comprising a drug with an exit in the wall for delivering the drug to a patient. In U.S. Pat. Nos. 4,008,719; 4,014,334; 4,058,122; 4,116,241; and 4,160,452 patentees Theeuwes and Ayer made available dosage forms comprising an inside and an outside wall made of poly(cellulose acylate) for delivering a dosage of drug to a patient in need thereof.

The history of the prior art dosage forms indicates a serious need exists for a novel and useful dosage form that provides an unexpected advancement in the science of dosage forms. For example, the prior art dosage forms lack the present ability to mask an unpleasant taste, they did not maintain the stability of a drug formulation, and the dosage forms did not protect a drug from oxidation. Then too, the drug formulation in the dosage form permitted the drug release profile to decline over time, thereby administering a nontherapeutic dose of drug. The wall of the dosage forms exposed to the gastrointestinal tract were lipophilic, they absorbed endogenous fats and consequently evidenced a decrease in structural integrity as seen in flaws or cracks in the wall. Moreover, the dosage forms wall and its drug formulation did not act in concert for providing a controlled

linear drug delivery profile over an extended time. Likewise, prior art dosage forms were formulated with water-leachable components within the membrane to control delivery rate of drug which water-leachable components diffused from the membrane against the direction of osmotic water flux making reproducibility and control of delivery rate patterns difficult, as seen in U.S. Pat. No. 5,160,744.

It is clear from the above presentation that a long-felt need exists for a dosage form comprising a walled structure and a drug formulation that function together for administering orally a drug at a controlled and sustained-release drug delivery profile with time. The need exists for a dosage form for administering a drug in a linear profile for treating infectious diseases, respiratory diseases, the cardiovascular system, blood and spleen, the digestive system, metabolic disorders, the endocrine system, the urogenital tract, sexually transmitted diseases, the nervous system, the locomotor system, psychiatric disorders and for providing symptomatic care. A dosage form is needed for replacing immediate-release dose-dumping forms administered three or four times daily. There are serious reasons for seeking a dosage form that replaces immediate-release forms, including a means for reducing peak-blood levels followed by a sharp drop in blood levels, a means for lessening side effects, a means for manufacturing the structural integrity of the dosage form, and a means for reducing the number of solvents used to manufacture the dosage form.

OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide both a novel and a useful dosage form that overcomes the disadvantages associated with the prior art.

Another object of the present invention is to satisfy a long-felt need by making available a dosage form that administers a drug in a linear profile over time.

Another object of the present invention is to provide a dosage form comprising a formulation comprising a drug and a first and second wall which formulation and walls operate together to deliver a drug in a linear rate over an extended time.

Another object of the invention is to provide a dosage form comprising an inside wall and an outside wall which outside wall protect the inside wall from the environment of the gastrointestinal tract.

Another object of the invention is to provide a bilayer wall that maintains its physical and chemical integrity during the administration of a drug.

Another object of the present invention is to provide a dosage form manufactured as an osmotic drug delivery device by standard manufacturing procedures into sizes, shapes and structures that represent an advancement in the drug delivery art.

Another object of the invention is to make available a dosage form comprising an outside bioprotective wall that shields the dosage form from injury and/or destruction in a gastrointestinal environment.

Another object of the invention is to provide a dosage form comprising ethylcellulose and a hydroxyalkylcellulose wall formed from a single solvent system.

Another object of the invention is to provide a dosage form comprising an interior wall comprising an ethylcellulose and a hydroxypropylalkylcellulose shielded by an exterior wall comprising a poly(cellulose acylate) and other wall-forming ingredients.

Another object of this invention is to provide a dosage form comprising an inside wall that comprises a hydrophobic polymer insoluble in the digestive system and hydrophilic polymer soluble in the digestive system which latter polymer dissolves from the wall thereby increasing the porosity and increasing the fluid flux of the wall.

Another object of the invention is to provide a transport mechanism whereby water-soluble flux enhancers within the interior wall during the operation of the dosage form are transported by diffusion from the wall in the same direction as the osmotic water-flow passing through the bilayer wall.

Another object of the invention is to provide a dosage form comprising an interior seamless wall that surrounds a formulation containing a drug, and an exterior seamless wall that surrounds the interior wall, which dual walls avoid a break-up in the gastrointestinal tract while keeping the structural integrity of the dosage form.

Another object of the invention is to provide a method for treating a patient with a medication administered from a controlled-release dosage form.

Another object of this invention is to provide a method for administering an effective dose of a medicament at a sustained release rate to provide a therapeutically effective blood level of the medicament for 30 minutes to 24 hours, which sustained release rate provided by the invention is free from changes induced by the environment of the gastrointestinal tract.

Another object of the invention is to provide a method for administering an opioid medicament from a sustained release dosage form into the gastrointestinal tract for producing an opioid medicament level in the blood of a patient for an extended time of 30 minutes to 24 hours, that is longer than the 0 to 4 hours provided by a conventional nonextended rapid-release dosage form.

Other objects, features, aspects, and advantages of the invention will be more apparent to those versed in the drug dispensing art from the following detailed specification taken in conjunction with the drawing figures and the accompanying claims.

BRIEF DESCRIPTION OF DRAWINGS

In the drawing figures, which are not drawn to scale, but are set-forth to illustrate various manufactures of the invention, the drawing figures are as follows:

Drawing FIG. **1**, is a general view of a dosage form provided by this invention, that is designed, shaped and adapted for the oral administration of a drug at a controlled rate over an extended time to a human patient in need of drug therapy.

Drawing FIG. **2**, is a general view of the dosage form of drawing FIG. **1**, in opened section, depicting a dosage form provided by this invention comprising an internally housed pharmaceutically-acceptable drug composition surrounded by an interior and exterior wall.

Drawing FIG. **3**, is an opened view of drawing FIG. **1**, illustrating a dosage form comprising a drug composition, and a separate but initially contacting push-displacement composition comprising means for pushing the drug composition from the dosage form with both compositions surrounded by an interior wall and an exterior wall.

Drawing FIG. **4**, is an opened view of the dosage form of drawing FIG. **1**, depicting the dosage form in operation as a fluid sensitive pore former begins to dissolve, and is eluted from the interior wall to increase the porosity of the interior wall, while simultaneously keeping the physical and chemical integrity of the exterior wall.

Drawing FIG. **5**, represents a plot of the dissolution of pore former candidates of the interior wall as a function of osmotic pressure.

Drawing FIGS. **6**, **7**, and **8** illustrate release patterns and comparison release patterns for dosage forms with different coating compositions.

In the drawing figures, and in the specification, like parts and like ingredients, are identified by like numbers. The terms that appear earlier in the specification, and in the description of the drawing figures, as well as in embodiments thereof, are further described in the specification.

DETAILED DESCRIPTION OF DRAWINGS

Turning attention now to the drawing figures in detail, which drawing figures are examples of a dosage form and a drug composition provided by this invention, and which examples are not to be construed as limiting the invention, one example of a dosage form is seen in drawing FIG. **1**. In drawing FIG. **1**, a dosage form **1** is seen comprising a body member **11** that comprises an exterior wall **12**. The exterior wall **12** surrounds an interior wall and an internal compartment, not seen in drawing FIG. **1**. Dosage form **10** comprises at least one exit **13** that connect the exterior environment, such as the gastrointestinal tract of a human patient, with the interior of the dosage form.

Dosage form **10**, of drawing FIG. **2**, illustrates a dosage form that possesses controlled-release delivery kinetics. The dosage form delivers a drug, or a drug and its pharmaceutically-acceptable salt to a patient in need of drug therapy. The phrase, controlled-release denotes the dosage form provides a linear drug release with time, or a zero order delivery rate of drug. Dosage form **10** controls or governs the delivery of drug **14**, represented by dots **14**, from an internal space or compartment **15**. Dosage form **10** delivers drug **14** at a measured rate per unit time over an extended or sustained-release time of six hours to twenty-four hours.

The dosage forms provided by this invention, are useful for establishing therapeutic drug levels in the blood, including the plasma, for therapy. Dosage form **10**, as seen in the accompanying figures, embraces the shape of a dosage tablet, and it can embrace the shape of a caplet, or a buccal, or a sublingual dosage form. The sustained-release dosage form of this invention provides extended-continuous delivery greater than conventional, noncontrolled tablets, or noncontrolled-nonsustained release tablets and/or capsules that exhibit a dose-dumping of their drug. Dosage form **10** of drawing FIG. **2**, comprises exterior wall **12** that surrounds compartment **15**. Exterior wall **12** comprises totally, or in at least a part a semi-permeable composition. The semipermeable composition is permeable to the passage of an aqueous or an aqueous-biological fluid present in the gastrointestinal tract, and wall **12** is impermeable to the passage of drug **14**. Wall **12** is nontoxic, and it maintains its physical and chemical integrity during the dispensing time of drug **14**. The phrase, maintains its physical and chemical integrity means wall **12** does not lose its structure, and it does not undergo a chemical change during the dispensing of drug **14**.

Wall **12** comprises a composition that does not adversely affect an animal, a human, or components of the dosage form. Compositions for forming wall **12** are, in one embodiment, comprised of a member selected from the group consisting a cellulose ester polymer, a cellulose ether polymer and a cellulose ester-ether polymer. These cellulosic polymers have a degree of substitution, DS, on the anhydroglucose unit, from greater than 0 up to 3 inclusive. By "degree of substitution" is meant the average number of

hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a substituting group. Representative wall **12** polymers comprise a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkanylates, mono-, and di- and tricellulose alkinylates. Exemplary polymers include cellulose acetate having a DS of up to 1 and an acetyl content of up to 31 weight %; cellulose acetate having a DS of 1 to 2 and any acetyl content of 21 to 35%; cellulose acetate having a DS of 2 to 3 and an acetyl content of 35 to 44.8%; and the like. More specific cellulosic polymers comprise cellulose propionate having a DS of 1.8, a propyl content of 39.2 to 45% and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a DS of 1.8, an acetyl content of 13 to 15% and a butryl content of 17% to 53% and a hydroxyl content of 0.5 to 4.7%; cellulose triacylates having a DS of 2.9 to 3, such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate and cellulose trioctanoate; celluloses diacylate having a DS of 2.2 to 2.6, such as cellulose disuccinate, cellulose dipalminate, cellulose dioctanoate, cellulose dipentanoate, co-esters of cellulose, such as cellulose acetate butyrate, and cellulose acetate propionate, and blends of the above.

Additional semipermeable polymers comprise acetaldehyde dimethylcellulose acetate; cellulose acetate ethylcarbamate; cellulose acetate methylcarbamate; cellulose diacetate propylcarbamate; cellulose acetate diethylaminoacetate; ethyl acrylate methyl methacrylate, semipermeable polyamide; semipermeable polyurethane; semipermeable sulfonated polystyrene; semipermeable crosslinked selective polymer formed by the coprecipation of a polyanion and polycation, as disclosed in U.S. Pat. Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006 and 3,546,876; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; semipermeable, lightly crosslinked polystyrenes; semipermeable crosslinked poly (sodium styrene sulfonate); semipermeable crosslinked poly (vinylbenzyltrimethyl ammonium chloride); and semipermeable polymers possessing a fluid permeability in the range of 2.5×10^{-8} to 5×10^{-2} (cm^2/hr·atm), expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable exterior wall **12**. The polymers are known to the polymer art in U.S. Pat. Nos. 3,845,770; 3,916,899 and 4,160,020; and in *Handbook of Common Polymers*, by Scott, J. R. and Roff, W. J. 1971, CRC Press, Cleveland, Ohio. Wall **12**, in a present manufacture can be coated from a substantially single solvent system, such as acetone if coated from a solution, or water if coated as a dispersion.

Dosage form **10** comprises an interior wall **16**. The interior wall **16** faces compartment **15**, and exterior wall **12**. Exterior wall **12** comprises a surface that faces the environment of use. Interior wall **16** comprises ethylcellulose, one hundred weight percent, (100 wt %), or in another manufacture a composition comprising a blend of 40 to 99 wt % ethylcellulose and 1 to 60 wt % hydroxyalkylcellulose with the total weight of the compositional blend equal to 100% wt. The ethylcellulose used for the interior wall is nontoxic, insoluble in water, and insoluble in gastrointestinal fluid. The interior ethylcellulose wall is coated from a single anhydrous solution, or the interior ethylcellulose wall is coated from a dispersion comprising the single solvent water. The ethylcellulose used for the purpose of this invention comprises a 15 to 60 weight percent ethoxy content, a viscosity of 4 to 200 centiposes, or higher, and a 5,000 to 1,250,000 weight average molecular weight. The hydroxyalkylcellulose comprises an alkyl of 1 to 5 carbons as represented by hydroxypropylcellulose. The hydroxypropylcellulose is homogeneously blended with the ethylcellulose, and is identified by a wavy line **17** in interior wall **16**. The hydroxypropylcellulose **17** in interior wall **16** comprises a 7,500 to 1,500,000 weight-average molecular weight, and it is soluble in water below 40° C. and in ethyl alcohol and displays a solubility in water which sensitive to osmotic pressure or ionic strength.

Interior wall **16** comprising hydroxypropylcellulose provides unexpected properties for this invention. For instance, ethylcellulose is hydrophobic and accordingly its fluid permeability is low which hinder sufficient water flux passing through wall **16** to provide a wide-range of delivery rates. This invention, enhances the fluid permeability of wall **16** by blending a hydrophilic fluid flux enhancer, which operates as a pore former in the first ethylcellulose wall. The hydrophilic enhancer increases the permeability of the ethylcellulose wall as it is dissolved and/or leached therefrom, to provide fluid-control pores. However, if the dosage form is manufactured with a single wall comprising a composition of ethylcellulose and hydroxypropylcellulose, as the pores are formed, the pores allow lipids which are present in the gastrointestinal tract to sorb into this unprotected wall, which leads to an unaccepted change in this nonprotected single wall. That is, the hydrophobic lipids cause the unprotected wall to become soft, flaccid and tearable as the lipid functions as a plasticizer within the ethylcellulose. The presence of the sorbed lipids cause the porous wall to become hydrophobic again, thereby reversing the desirable effects of the hydrophilic flux enhancer. The present invention unexpectedly discovered by providing an outside wall comprising a cellulose acylate, the outside wall excludes and prevents the lipids of the gastrointestinal tract from contacting and reaching the interior wall. The interior ethylcellulose-hydroxypropylcellulose-exterior cellulose acylate bilayer wall provides a wide range of low to high fluxes. An additional advantage provided by the present invention is each wall can be coated from a single solvent to provide reproducible interior and exterior walls with reproducible permeability and mechanical properties.

In drawing FIG. **2**, internal compartment **15** comprises a single homogenous composition. The compartment **15** comprises therapeutic agent **14**, represented by dots. The term therapeutic agent as used herein included medicines or drugs, nutrients, vitamins, food supplements, and other beneficial agents that provide a therapeutic or a benefit to animals, including a warm-blooded animal, humans, farm animals, and zoo animals. Representative of drugs **14** comprises an opioid analgesic selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridne, benzylmorphine bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, diepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazone, ethoheptazine, ethylmethylthiambutene, ethylmorphine, propylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroenitabas, hydrocypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone,

phenomorphone, phenazocine, phenoperidine, piminodine, pirtramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, and tilidine. The dose of opioid drug **14** is 0.1 μg to 700 mg.

The opioid analgesic **14** can be present in compartment **15** alone, or the opioid analgesic **14** can be present with a nonopioid analgesic **14**. Examples of nonopioid analgesic comprise a member selected from the group consisting of acetaminophen, aminobenzoate potassium, aminobenzoate sodium, aspirin, benoxaprofen, benzydamine, bicifadine decibuprofen, fenoprofen, flurbiprofen, ibufenac, indoprofen, ibuprofen, ketoprofen, naproxen, naproxol, salicylamide, sodium salicylate, and salicylate potassium. The dose of nonopioid analgesic **14** is 0.5 mg to 600 mg. An analgesic composition in compartment **15** comprises 1.0 mg to 750 mg of both the opioid analgesic and nonopioid analgesic.

The analgesic drug comprising the opioid analgesic and the nonopioid analgesic can be present as the free base, free acid, or as a therapeutically acceptable derivative, or as a therapeutically acceptable salt. The therapeutically acceptable salts comprise inorganic salts, organic salts, including hydrobromide, hydrochloride, mucate, N-oxide, sulfate, acetate, phosphate dibasic, phosphate monobasic, acetate trihydrate, bi(heptafluorobutyrate), bi(methylcarbamate), bi(pentafluoropropionate), bi(pyridine-3-carboxylate), bi(trifluoroacetate), bitartrate, chlorhydrate, and sulfate pentahydrate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methyinitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, and procaine, aluminum, calcium, lithium, magnesium, potassium, sodium propionate, zinc, and the like.

Dosage form **10**, in compartment **15** comprises a pharmaceutically acceptable polymer hydrogel **18**, as represented by horizontal dashes. Representative polymer hydrogels comprise a maltodextrin polymer comprising the formula $(C_6H_{12}O_5)\lambda \cdot H_2O$, wherein λ is 3 to 7,500, and the maltodextrin polymer comprises a 500 to 1,250,000 number-average molecular weight; a poly(alkylene oxide) represented by poly(ethylene oxide) and poly(propylene oxide) having a 50,000 to 750,000 weight-average molecular weight, and more specifically represented by a poly(ethylene oxide) of at least one of 100,000, 200,000, 300,000, or 400,000 weight-average molecular weights; an alkali carboxyalkylcellulose, wherein the alkali is sodium, lithium, potassium or calcium, and alkyl is 1 to 5 carbons such as methyl, ethyl, propyl or butyl of 10,000 to 175,000 weight-average molecular weight; and a copolymer of ethylene-acrylic acid, including methacrylic and ethacrylic acid of 10,000 to 1,500,000 number-average molecular weight. The therapeutic composition comprises 5 to 400 mg of a polymer hydrogel. The therapeutic composition can be manufactured into dosage form **10** and it can be used as the therapeutic composition for its therapeutic effect. The hydrogel polymer exhibits an osmotic pressure gradient across bilayer interior wall and exterior wall thereby imbibing fluid into compartment **15** to form a solution or a suspension comprising drug **14** that is hydrodynamically and osmotically delivered through a passageway from dosage form **10**.

Dosage form **10** comprises a binder **19** represented by vertical dashes **19**. The binder imparts cohesive qualities to the composition. Representative materials useful for this invention as binders comprise a member selected from the group consisting of starch, gelatin, molasses, a vinyl polymer comprises 5,000 to 350,000 viscosity-average molecular weight, represented by a member selected from the group consisting of poly-n-vinylamide, poly-n-vinylacetamide, poly(vinyl pyrrolidone), also known as poly-n-vinylpyrrolidone, poly-n-vinylcaprolactone, poly-n-vinyl-5-methyl-2-pyrrolidone, and poly-n-vinylpyrrolidone copolymers with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laureate, and vinyl stearate, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and mixtures of binders. The binders can be used as a solution, or in a dry form to prepare the therapeutic composition. The therapeutic composition comprises 0 to 100 mg of a binder and in a present manufacture from 0.01 to 50 mg of the binder.

Dosage form **10** comprises a lubricant **20** represented by the letter v. The lubricant is used during manufacture of the composition to prevent sticking to die walls or punch faces, generally to lessen adhesion. The lubricants are selected from the group consisting of polyethylene glycol, sodium stearate, oleic acid, potassium oleate, caprylic acid, sodium stearyl fumarate, magnesium palmitate, calcium stearate, zinc stearate, magnesium stearate, magnesium oleate, calcium palmitate, sodium suberate, potassium laureate, stearic acid, salts of fatty acids, salts of alicyclic acids, salts of aromatic acids, oleic acid, palmitic acid, a mixture of a salt of a fatty, alicyclic or aromatic acid, and a mixture of magnesium stearate and stearic acid. The amount of lubricant in the therapeutic composition is 0.01 to 20 mg.

Drawing FIG. **3** depicts dosage form **10** in opened section illustrating internal compartment **15**. Internal compartment comprises the therapeutic composition containing drug **14**, as described in detail in drawing FIG. **2**. The therapeutic composition of drawing FIG. **2** is identified further in drawing FIG. **3** as drug layer **21**. Drug layer **21** comprises the ingredients described in drawing FIG. **2** and the details previously disclosed are included in this description of drawing FIG. **3**. Drug layer **21** in drawing FIG. **3** initially is in contact with push layer **22**.

In drawing FIG. **3**, push layer **22** comprises 10 mg to 400 mg of an expandable osmopolymer **23** represented by squares. The osmopolymer **23** in layer **22** possesses a higher molecular weight than the hydrogel polymer **18** in the drug composition. The osmopolymer **23** comprises a member selected from the group consisting of a polyalkylene oxide and, a carboxyalkylcellulose and acrylates. The polyalkylene oxide possesses a 1,000,000 to 10,000,000 weight-average molecular weight. Representative of polyalkylene oxide include a member selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene oxide having a 1,000,000 molecular weight, polyethylene oxide possessing a 2,000,000 molecular weight, polyethylene oxide comprising a 3,000,000 to 8,000,000 molecular weight, polyethylene oxide comprising a 7,000,000, and 7,800,000 molecular weight, and cross-linked polymethylene oxide possessing a 1,000,000 molecular weight, and polypropylene oxide of 1,200,000 molecular weight. Typical osmopolymer **23** carboxyalkylcellulose in the expandable layer **22** comprises a 200,000 to 7,250,000

weight-average molecular weight. Representative carboxyalkylcellulose comprises a member selected from the group consisting of alkali carboxyalkylcellulose, sodium carboxymethylcellulose, lithium carboxyethylcellulose, calcium carboxymethylcellulose, potassium carboxymethylcellulose, sodium carboxyethylcellulose, lithium carboxyalkylhydroxyalkylcellulose, sodium carboxyethylcellulose, carboxyalkylhydroxyalkylcellulose, carboxymethylhydroxyethylcellulose, carboxethylhyd roxyethylcellulose and carboxymethylhydroxypropylcellulose. Typical osmopolymer **23** acrylates comprise non-crosslinked polyacrylic acid, and polyacrylic acids crosslinked with allyl sucrose, allylpentacrythritol, or divinyl glycol, sodium or potassium polyacrylic acid, and the like. The osmopolymers used for the push-expandable layer exhibit an osmotic pressure gradient across semipermeable wall **12**. The osmopolymers imbibe fluid into dosage form **10**, thereby swelling, expanding as a hydrogel or osmogel, whereby, they push the drug from the osmotic dosage form.

Push layer **22** comprises 0 to 200 mg, and presently 0.5 to 75 mg of an osmotically effective compound **24**, represented by circles. The osmotically effective compounds are known also as osmagents and as osmotically effective solutes. They imbibe an environmental fluid, for example, from the gastrointestinal tract, into dosage form **10** for contributing to the delivery kinetics of push layer **22** and to the permeability characteristics of the interior wall **16**. Representative of osmotically active compounds comprise a member selected from the group consisting of osmotic salts, such as sodium chloride, potassium chloride, magnesium sulfate, lithium phosphate, lithium chloride, sodium phosphate, potassium sulfate, sodium sulfate, potassium phosphate, osmotic carbohydrates; glucose, fructose, maltose and sorbitol; urea; osmotic acids; tartaric acid; citric acid; potassium acid phosphate; and a mixture of sodium chloride and urea.

Push layer **22** comprises 0 to 75 mg of a suspending agent used for providing stability and homogenicity to push layer **22**. Suspending agent **25**, represented by clear triangles comprises a hydroxypropylalkylcellulose that comprises an alkyl of 1 to 7 carbons, straight or branched, with the hydroxypropylalkylcellulose possessing a 9,000 to 450,000 number-average molecular weight. The hydroxypropylalkylcellulose is represented by a member selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose and hydroxypropylpentylcellulose. Push layer **22** optionally comprises a hydroxyalkylcellulose, also represented by triangles **25**. The hydroxyalkylcellulose is a viscosity-increasing suspending agent comprises a member selected from the group consisting of hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose comprising a 7,500 to 1,000,000 viscosity-average molecular weight. The suspending agent include also polyvinylpyrrolidone, acacia, agar, locust bean gum, alginic acid, gum karaya, gum tragacaroth, carrageenan, gum ghatti, guar gum, xanthan gum, and bentonite.

Push layer **22** comprises 0 to 5 mg of a nontoxic colorant, or dye **26** identified by a half-circle. The colorant **26** makes the dosage form more esthetic in appearance, and it serves to identify the dosage form during manufacture and during therapy. The colorants include Food and Drug Administrations Colorant (FD&C), such as FD&C No. 1 blue dye, FD&C No. 4 red dye, FD&C yellow No. 5, FD&C yellow No. 6, FD&C blue No. 2, FD&C green No. 3, FD&C cranberry red No. 40, red ferric oxide, yellow ferric oxide, black ferric oxide, titanium dioxide, carbon black, Opadry® comprising polycellulose, or starch, or cured polymers with dyes commercially available from Colorcon Corporation, West Point, Pa.; erythrosine, allura red, sunset yellow and chlorophylls.

A lubricant **27**, identified by hexagon is formulated into push-expandable layer **22**. Typical lubricants comprise a member selected from the group consisting of polyethylene glycol, sodium stearate, potassium stearate, magnesium stearate, stearic acid, calcium stearate, sodium oleate, calcium palmitate, sodium laurate, sodium ricinoleate, potassium linoleate, glyceryl monstearate, glyceryl palmitostearate, halogenated castor oil, sodium lauryl sulfate, sodium stearyl fumarate, and zinc stearate. The amount of antiadherent lubricant in layer **22** is 0.01 to 10 mg.

An antioxidant **28**, represented by right slanted dashes, is present in push-expandable formulation **22** to inhibit the oxidation of ingredients comprising expandable formulation **22**. Expandable formulation **22** comprises 0.00 to 5 mg of an antioxidant. Representative antioxidants comprise a member selected from the group consisting of absorbic acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaretic acid, potassium sorbate, sodium ascorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2-,6-ditertiary butylphenol, alphatocopherol, and propylgallate. The antioxidant slow, or prevent the oxidization of the dosage form and its ingredients by atmospheric oxygen.

Dosage form **10**, comprises another manufacture provided by the invention. Dosage form **10** comprises an overcoat not shown on the outer surface of wall **12** of dosage form **10**. The overcoat is a therapeutic composition comprising 0.5 to 200 mg of drug and 0.5 to 275 mg of a pharmaceutically acceptable carrier selected from the group consisting of alkylcellulose, hydroxyalkylcellulose and hydroxypropylalkylcellulose. The overcoat is represented by methylcellulose, hydroxyethylcellulose, hydroxybutylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxypropylethylcellulose and hydroxypropylbutylcellulose. The overcoat, carried by the outer surface of the exterior wall **12** distant from the compartment **15** and it can be formulated with 0 to 50 wt % of a plasticizer, opacificer, colorant, or antitack agent, not seen in drawing FIG. **4**. The overcoat provides therapy immediately as the overcoat dissolves or undergoes dissolution in the presence of gastrointestinal fluid and concurrently therewith delivers the drug into the gastrointestinal tract for immediate drug therapy.

Dosage form **10**, manufactured as an osmotically controlled-release dosage form, comprises at least one passageway **13**. The phrase "controlled-release" as used herein indicates that control is exercised over both the duration and the profile of the drug release pattern. The expression "passageway" as used for the purpose of this invention, includes aperture, orifice, bore, pore, porous element through which drug **14** can be pumped, diffuse or migrate through a fiber, capillary tube, porous overlay, porous insert, microporous member, and porous composition. The passageway **13** includes also a compound that erodes or is leached from wall **12** in the fluid environment of use to produce at least one passageway. Representative compounds for forming a passageway include erodible poly(glycolic) acid, or poly(lactic) acid in the wall; a gelatinous filament; a water-removable poly(vinyl alcohol); leachable com-

pounds such as fluid-removable pore-forming polysaccharides, acids, salts, or oxides. A passageway can be formed by leaching a compound from wall **12**, such as sorbitol, sucrose, lactose, maltose or fructose, to form a controlled-release dimensional pore-passageway. The passageway can have any shape, such as round, triangular, square and elliptical, for assisting in the controlled-metered release of drug **14** from the dosage form. The dosage form can be manufactured with one or more passageways for example two passageways, in spaced-apart relation on one or more surfaces of the dosage form. A passageway and equipment for forming a passageway are disclosed in U.S. Pat. Nos. 3,845,770 and 3,916,899 by Theeuwes and Higuchi; in U.S. Pat. No. 4,063,064 by Saunders et al.; and in U.S. Pat. No. 4,088,864 by Theeuwes et al. Passageways comprising controlled-release dimensions sized, shaped and adapted as a releasing-pore formed by aqueous leaching to provide a releasing-pore of a controlled-release rate are disclosed in U.S. Pat. Nos. 4,200,098 and 4,285,987 by Ayer and Theeuwes.

Drawing FIG. **4** illustrates dosage form **10** in operation during a drug **14** delivery period. The illustrated dosage form **10** comprises an outer wall **12** and an inner wall **16**. The outer wall **12** maintains its physical and chemical integrity throughout the drug delivery period. Inner wall **16** comprises a pore former **29** that is aqueous soluble at an osmotic pressure of 8 atmospheres, which 8 atmospheres generally is the osmotic pressure of the gastrointestinal tract of a human. The pore former **29**, in one manufacture, is a pharmaceutically acceptable polymer that exhibits an aqueous solubility which is sensitive to osmotic pressure, which polymer is soluble at low osmotic pressure and insoluble or slowly soluble at higher osmotic pressure. Representative of other acceptable pore formers include alkali metal salts such as lithium carbonate, sodium chloride, potassium chloride, and potassium sulfate; alkaline earth metal salts such as calcium phosphate, and calcium nitrate; transition metal salts such as ferric chloride, ferrous sulfate, and zinc sulfate; polysaccharides including mannitol, mannose, galactose, aldohexose, altrose, talose and sorbitol. The osmotic pressure can be measured by Model 302B, Vapor Pressure Osmometer, manufactured by the Hewlett Packard, Co., Avondale, Pa. A pore forming polymer is represented by hydroxypropylcellulose possessing a weight-average molecular weight of 80,000 grams per mole. Dosage form **10**, when initially placed into an aqueous environment, or into a fluid biological environment, exhibits a slow drug delivery until pore former **29** dissolves or is leached from inner wall **16**. For example, after a period of time, often 1 to 2 hrs, the osmotically-sensitive pore former **29** begins to dissolve and is eluted from inner wall **16**. This operation, provides a continuous and seamless inner pore wall **16** with pore former **29** being hydrodynamically and osmotically pumped as seen by multi-arrows **30** from dosage form **10**. The eluted pore former **29** causes the permeability of inner wall **16** to increase, which correspondingly causes the net permeability of bilaminated inner wall **16**-outer wall **12** to increase over time. This unexpected result provided by this invention, with its increase in permeability offsets any decrease in osmotic activity and produces a linear drug delivery profile. The permeability of a wall can be measured according to a procedure which involves measuring the flow of water through the membrane as a result of osmotic driving force. The measurement is first conducted with a single layer membrane which represents the exterior wall, then the measurements are conducted with bilayer membranes with the exterior and interior walls in parallel arrangement. First, an exterior wall membrane is clamped in a vertical orientation between the two chambers which are commonly referred to as Franz cells. One chamber is filled with distilled water which has an osmotic pressure of zero while the adjoining chamber is filled with a solution of known osmotic pressure, such as a saturated solution of potassium chloride which has an osmotic pressure of 245 atmospheres or of saturated lactose solution which has an osmotic pressure of 20 atmospheres. The osmotic pressure of such osmotic reference solutions are measured using standard freezing point depression measurements or vapor pressure osmometry. Vapor pressure osmometers are available, for example, from Knauer & Co GMBH, Berlin, West Germany. The membrane is thus exposed on one side to pure water and exposed to the osmotic reference solution on the opposite side. Prior to making measurements, a graduated pipette is attached to the chamber holding the osmotic reference solution. Both chambers also contain magnetic stirrers and both chambers are also immersed in a thermal jacket. While measurements are taken, both cells are stirred by way of an external magnetic stirrer and both are maintained at a fixed temperature. The fixed temperature is maintained by continuously passing a thermostated fluid, such as water at 37° centigrade, through the thermal jacket. The Franz cells and stirring equipment are available from Crown Glass Company, Somerville, N.J.

Water is imbibed by osmosis from the pure water side through the membrane to the solution side. The rate of water flowing through the membrane is measured by monitoring the volumetric flow as a function of time as reflected in the rise in column of solution within the graduated pipette. The thickness and exposed surface area of the membrane are also measured. These dimensional measurements are performed with standard measuring instruments such as with calipers or a tool maker's microscope. Then, given the volumetric flow rates and these measurements, the osmotic permeability of the external wall, K_e, is calculated according to the following Equation as:

$$K_e = \frac{(dV/dt)h_e}{\pi A} \quad (1)$$

where (dV/dt)=volumetric flow rate
h_e=membrane thickness of the exterior wall
Π=osmotic pressure
Π_A=membrane area

After the permeability of the exterior wall is determined, the bilayer membrane is then mounted in the Franz cell. The bilayer wall is oriented such that the interior wall faces the osmotic reference solution and the exterior wall faces the pure water reference. The osmotic water flux is then measured across the bilayer membrane according to the above procedures. The osmotic water flux is inversely proportion to the series resistance provided by the exterior wall and the interior wall and directly proportional to the osmotic pressure, as described by Equation 2:

$$dV/dt = \frac{\pi}{(h_e/K_eA) + (h_i/K_iA)} \quad (2)$$

where h_e=thickness of exterior wall
K_e=permeability of exterior wall
h_i=thickness of interior wall
K_i=permeability of interior wall

Rearranging Equation 2 yields the permeability of the interior wall, Equation 3:

$$K_i = \frac{h_i(dV/dt)}{[\pi A + (h_e/K_e)(dV/dt)]} \quad (3)$$

Given the measured values of volumetric flow rate, thicknesses of the interior wall and exterior wall, the known value for the permeability of the exterior wall, and measured osmotic pressure, the permeability of the interior wall is then calculated from Equation 3. Osmotic reference values of various values ranging from 0 as represented by distilled water to 445 atmospheres as represented by saturated aqueous urea solution can be tested in this format to characterize the effect of osmotic pressure on the permeability of the bilayer membrane wall. In addition to osmotic pressure, the effect of ionic strength on the permeability of the bilayer wall can be measured. The measurements, in this instance, performed with reference solutions of known ionic strength against the distilled water reference as above. The ionic strength of the solution, μ, can be calculated according to standard equations of physical chemistry such as Equation 4:

$$\mu=0.5[C_1Z_1^2+C_2Z_2^2+C_3Z_3^2+\ldots] \quad (4)$$

where C_x represents the molar concentration of any ion x in the solution and Z_x represents the corresponding valence of ion x. Reference solutions of a simple salt such as sodium chloride can be prepared as the ionic strength reference. Since the value of each ionic charge Z is unity for sodium chloride, a value of one for the sodium ion and a value of one for the chloride ion, the ionic strength according to Equation 4 is directly proportional to molar concentration. A saturated solution of sodium chloride consists of 5.5 moles per liter and therefore has an ionic strength of 5.5 moles per liter. Such a saturated solution can be serially diluted with distilled water to produce a series of ionic strength reference solutions of any value less than 5.5 moles per liter for use in the reference cell to determine the effect of ionic strength on bilayer permeability as a function of ionic strength.

Pore forming materials which have solubilities sensitive to osmotic pressure or to ionic strength can be screened experimentally prior to formulating them as pore formers within the interior wall. This procedure involves forming an aqueous solution of the candidate pore former using distilled water as the solvent. Then, the resulting solution is cast onto a smooth inert surface, such as a glass plate, and allowed to dry to a film. The film is then removed and cut into sections of known area, thickness, and weight. The resulting film samples are then placed in a series of reference solutions of various osmotic pressures or ionic strengths with mild stirring. The time required for the film to dissolve, t, is then measured as a function of osmotic pressure or ionic strength. Then, given the known values of initial film thickness, h_i, the dissolution rate of the film, dh/dt, can be calculated according to Equation 5. The factor 2 is introduced to account for simultaneous dissolution from both sides of the film.

$$dh/dt=h_i/2t \quad (5)$$

This screening can also be expanded to include the effect of molecular weight of the pore former on dissolution rate as a function of osmotic pressure or ionic strength. This can be accomplished by determining the dissolution rate of low molecular weight and high molecular weight pore formers which effect generally follows the trend of faster dissolution rate at lower molecular weight and faster dissolution rate at lower osmotic pressure.

Drawing FIG. **5** demonstrates the dissolution behavior in the presence of osmotic pressure. The x-axis refers to the osmotic pressure of the test media and the y-axis represents the dissolution rate of pore former under the influence of osmotic pressure. The different symbols represent different molecular weight pore formers initially present within an internal wall. The dark circle represents 80,000 g/mole, the clear circle 190,000 g/mole, the dark triangle 300,000 g/mole, and the clear triangle 1,000,000 g/mole.

DESCRIPTION FOR MANUFACTURING THE COMPOSITION AND DOSAGE FORM OF THE INVENTION

The interior wall **16** and the exterior wall **12** of the dosage form can be formed by using an air suspension procedure. This procedure consists in suspending and tumbling a wall-forming composition in a current of air and wall-forming composition until a wall is applied to the drug-forming compositions. The interior wall is formed first followed by the exterior wall. The air suspension procedure is well-suited for independently forming an individual wall. The walls can be formed with a wall-forming composition in a Wurster® air suspension coater. The interior wall can be formed using the solvent ethanol. The exterior wall is formed using an organic solvent, such as acetone-water cosolvent 90:10 to 100:0 (wt:wt) and with 2.5 wt % to 7 wt % polymer solvents. An Aeromatic® air suspension coater can be used for applying both the walls, the interior wall and the exterior wall in successive applications.

Other forming technologies, such as pan coating, can be used for providing the dosage form. In the pan coating system, wall-forming compositions are deposited by successive spraying of the composition or the bilayered wall-arrangement, accompanied by tumbling in a rotating pan. A larger volume of cosolvent can be used to reduce the concentration of polymer solids to produce a thinner wall. Finally, the walls of the coated compartments are laser or mechanically drilled, and then dried in a forced air or humidity oven for 1 to 3 days or longer to free the solvent from the dosage form. Generally, the walls formed by these technologies have a thickness of 2 to 20 mils (0.051 to 0.510 mm) with a presently preferred thickness of 2 to 10 mils (0.051 to 0.254 mm).

The dosage form of the invention in another embodiment is manufactured by standard manufacturing techniques. For example, in one manufacture the beneficial drug and other ingredients comprising a therapeutic composition or comprising the drug layer facing the exit means are blended, or the ingredients are blended then pressed, into a solid layer. The drug and other ingredients can be blended with a solvent and formed into a solid or semisolid formed by conventional methods such as ball-milling, calendaring, stirring or roll-milling and then pressed into a selected shape. The drug layer posses dimensions that correspond to the internal dimensions of the area the drug layer is to occupy in the dosage form. Next, the drug layer is placed in contact with the push-displacement layer prepared in a like manner. The layering of the drug layer and the push-displacement layer can be fabricated by conventional press-layering techniques. The bilayers possess dimensions corresponding to the dimensions of the internal compartment of the dosage form. Finally, the two-layer compartment forming members are surrounded and coated with an inner and outer walls. A passageway is laser drilled or mechanically drilled through the walls to contact the drug layer, with the dosage form optically oriented automatically by the laser equipment for forming the passageway on the preselected drug surface.

In another manufacture, the dosage form is manufactured by the wet granulation technique. In the wet granulation

technique the drug and the ingredients comprising the drug layer are blended using a solvent, such as isopropyl alcohol as the granulation fluid. Other granulating fluid, such as water, or denatured alcohol 100% can be used for this purpose. The ingredients forming the drug layer are individually passed through a 40 mesh screen and then thoroughly blended in a mixer. Next, other ingredients comprising the layer are dissolved in a portion of the granulation fluid, such as the solvent described above. Then, the latter prepared wet blend is slowly added to the drug blend with continual mixing in the blender. The granulating fluid is added until a wet blend mass is produced, which wet mass is then forced through a 20 mesh screen onto oven trays. The blend is dried for 18 to 24 hours at 25° C. to 40° C. The dry granules are then screened with a 16 mesh screen. Next, a lubricant is passed through a 60 mesh screen and added to the dry screened granule blend. This procedure is followed for the push-displacement composition. The granulation in both instances, are put into mixing containers and tumble mixed for 2 to 10 minutes. The drug and the push composition are layered and pressed into a layered tablet, for example in a Manesty® layer press.

Another manufacturing process that can be used for providing the drug and push-displacement compositions comprise blending their powdered ingredients in a fluid bed granulator. After the powdered ingredients are dry blended in the granulator, a granulating fluid, for example, poly (vinylpyrrolidone) in a solvent, such as in water, is sprayed onto the respective powders. The coated powders are then dried in a granulator. This process coats the ingredients present therein while spraying the granulating fluid. After the granules are dried, a lubricant, such as stearic acid or magnesium stearate, is blended as above into the mixture. The granules are then pressed in the manner described above. In another embodiment, when the fluid in granulating process is used to manufacture the push-displacement layer, an antioxidant present in the polyalkylene oxide can be removed during the processing step. If antioxidant is desired, it can be added to the push-displacement layer, and this can be accomplished during the fluid bed granulation described above.

The dosage form of this invention is manufactured in another embodiment by mixing a drug with composition-forming ingredients and pressing the composition into a solid layer possessing dimensions that correspond to the internal dimensions of the compartment space adjacent to a passageway. In another embodiment, the drug and other drug composition forming ingredients and a solvent are mixed into a solid, or semi-solid, by conventional methods such as ball-milling, calendaring, stirring, or roll-milling, and then pressed into a preselected, layer-forming shape.

In the general manufactures as presented herein, the manufacture comprising a drug and compositional forming ingredients are placed in contact with the push-displacement layer, and the drug layer and the push layers are surrounded then with the bilayered walls. The layering of the drug composition and the push-displacement composition can be accomplished by using a conventional two-layer tablet press technique. The walls can be applied by molding, spraying or dipping the pressed shapes into wall-forming materials. Another technique that can be used for applying the walls is the air-suspension wall-forming procedure. This procedure consists in suspending and tumbling the two layered drug-push core in a current of air until the wall-forming composition are applied separately to the compartment drug-push layers. Manufacturing procedures are described in *Modern Plastics Encyclopedia*, Vol. 46, pp. 62–70 (1969); and in *Pharmaceutical Sciences*, by Remington, 14th ed., pp. 1626–1648 (1970) published by Mack Publishing Co., Easton, Pa. The dosage form can be manufactured by following the teaching the U.S. Pat. Nos. 4,327,725; 4,612,008; 4,783,337; 4,863,456; and 4,902,514.

DETAILED DISCLOSURE OF EXAMPLES

The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure and the accompanying claims.

EXAMPLE 1

The solubility of pore former candidates to osmotic pressure was evaluated. First, aqueous solutions of the pore former candidate hydroxypropylcellulose commercially-available from Hercules, Wilmington, Del., under the trade name Klucel® were prepared using grades of different molecular weights. The solutions were prepared with molecular weights of 80,000 grams per mole, 300,000 and 1 million grams per mole using Klucel EF, GF and HF, respectively. An intermediate molecular weight of 190,000 grams per mole was also generated by blending equal weight portions of the EF and GF grades. The resulting solutions were then cast on glass plates and dried at room temperature. The resulting films were removed from the plates and a discs of 2.4 cm^2 area were punched from the films. Thicknesses of the discs were measured with a table micrometer. Four discs of each molecular weight type were then individually bagged in nylon mesh bags having 12 openings per inch and attached to a plastic rod. The discs were then immersed in individual solutions of the nonionic sugar, sorbitol, at concentrations of 0, 182, 274, and 547 mg per milliliter thermostated to 37 degrees centigrade corresponding to a series of osmotic pressure values of 0, 30, 48, and 125 atmospheres, respectively, and oscillated with a frequency of 30 cycles per minute at an amplitude of 2 centimeters. The experiment was conducted in 4 by 4 experimental matrix such that each molecular weight type was tested in each osmotic pressure reference. The time to dissolution was then monitored for each sample. Dissolution rate was calculated according to Equation 5 and plotted as a function of osmotic pressure for each molecular weight. The data are plotted in FIG. 5. Based on these measurements, it was determined that the hydroxypropylcellulose having the lowest molecular weight of the series is insoluble above 30 atmospheres and soluble at an osmotic pressure between 0 and 30 atmospheres. This candidate pore former was used in subsequent membrane formulations of the osmotically-sensitive interior wall of bilayer membranes of the invention.

EXAMPLE 2

A novel, therapeutic composition comprising hydromorphone and acetaminophen, wherein the hydromorphone is a member selected from the group consisting of hydromorphone pharmaceutically acceptable base and hydromorphone pharmaceutically acceptable salt is prepared as follows: first, 175 g of hydromorphone hydrochloride, 500 g of acetaminophen, 647.5 g of poly(ethylene oxide) possessing a 100,000 molecular weight, and 43.75 g of poly (vinylpyrrolidone) having an average molecular weight of 40,000 are added to a mixing bowl and the ingredients dry mixed for 10 minutes. Then, 331 g of denatured, anhydrous alcohol is added slowly to the blended ingredients with

continuous blending for 10 minutes. Next, the freshly prepared granulation is passed through a 20 mesh screen, allowed to dry at 25° C. for about 20 hours, and then passed through a 16 mesh screen. Next, the granulation is transferred to a mixer, and lubricated with 8.75 g of magnesium stearate to produce a therapeutic hydromorphone acetaminophen composition. The therapeutic composition is compressed into tablets comprising 35 mg of hydromorphone hydrochloride and 100 mg of acetaminophen. The tablets are compressed under 2 tons of pressure.

EXAMPLE 3

The hydromorphone-acetaminophen analgesic tablets are coated with an interior wall then coated by an exterior wall as follows: first, 154 g of ethyl cellulose having a molecular weight of 220,000 grams per mole and an ethoxyl content of 48.0 to 49.5 weight percent, and 112 g of hydroxypropylcellulose having a 80,000 molecular weight and a molar substitution of 3, and then 14 g of polyoxyethylene (40) stearate were dissolved with stirring in 3,720 g of anhydrous ethanol. The solution resulting was allowed to stand without stirring for 3 days, to provide the interior wall-forming composition. Next, the exterior wall forming composition was prepared by dissolving 162.5 g of cellulose acetate having an acetyl content of 39.8 wt % and a molecular weight of 40,000 grams per mole, and 87.5 g of ethylene oxide-propylene oxide-ethylene oxide triblock copolymer having a molecular weight of approximately 8,400 grams per mole and an ethylene oxide content of 82 wt % in 4,750 g of anhydrous acetone with stirring and slight warming to 26° C. The resulting exterior forming wall composition was allowed to stand at ambient room temperature for one day.

Next, the analgesic tablets are placed into a pan coater. The interior wall-forming solution was sprayed onto the tablets in a current of warm air until a wall with a thickness of 6 mils (0.152 mm) was applied to the tablets. The interior ethylcellulose-hydroxypropylcellulose wall coated tablets were dried in a forced air oven at 40° C. for 24 hrs. Then, the interior coated tablets were returned to the pan coater and the exterior wall forming coat was sprayed onto the interior coated tablet to a thickness of 3 mils (0.0762 mm). Next, the biwalled tablets were dried and a round exit port having a diameter of 30 mils (0.762 mm) was drilled through the biwalls to provide a controlled-extended release dosage form.

EXAMPLE 4

Therapeutic compositions are manufactured by following the procedure of Example 2, to provide analgesic compositions comprising 1 mg to 1000 mg of an opioid selected from the group consisting of hydromorphone, hydromorphone base, hydromorphone salt, and hydromorphone derivatives; at least one nonopioid analgesic of 1 to 1000 mg selected from the group consisting of acetaminophen, aspirin, flurbiprofen, ibuprofen, indoprofen, benoxaprofen, propoxyphene, salicylamide, zenazocine and zomepirac; with the dose of opioid and nonopioid analgesic in the composition comprising 2 mg to 1000 mg; at least one polymeric carrier for both the opioid and nonopioid analgesics selected from 10 mg to 500 mg of a poly(alkylene oxide) comprising a 100,000 to 500,000 molecular weight represented by poly(methylene oxide), poly(ethylene oxide), poly(propylene oxide), poly(isopropylene oxide) and poly (butylene oxide); or a polymeric carrier of 10 mg to 500 mg of a carboxymethylene having a 7,500 to 325,000 molecular weight represented by a member selected from the group consisting of an alkali carboxymethylcellulose, and potassium carboxymethylcellulose, calcium carboxymethylcellulose, and potassium carboxymethylcellulose; 0.5 mg to 50 mg of a poly(vinyl) polymer possessing a 5,000 to 300,000 molecular weight as represented by poly(vinyl pyrrolidone),copolymer of poly(vinyl pyrrolidone and vinyl acetate), copolymer of poly(vinyl pyrrolidone and vinyl chloride), copolymer of vinyl pyrrolidone and vinyl fluoride), copolymer of poly(vinyl pyrrolidone and vinyl butyrate), copolymer of poly(vinyl pyrrolidone and vinyl laurate) and copolymer of poly(vinyl pyrrolidone and vinyl stearate); and 0 to 7.5 mg of a lubricant represented by a member selected from the group consisting of polyethylene glycol magnesium stearate, calcium stearate, potassium oleate, sodium stearate, stearic acid, and sodium palmitate. The therapeutic opioid-nonopioid dual analgesic composition may contain other composition forming ingredients, for example, colorants, compression aids such as microcrystallinecellulose, and binders such as starch. The analgesic composition can be compressed at a ⅛ to 3 ton-force to yield an orally administrable tablet.

EXAMPLE 5

The therapeutic analgesic composition is manufactured into an extended-sustained-linear release dosage form by providing the analgesic composition with an interior wall, an exterior wall and a passageway as set forth in Example 2.

EXAMPLE 6

A novel and useful therapeutic composition comprising 432 g of a morphine selected from the group consisting of morphine base, morphine pharmaceutically acceptable salt, pharmaceutically acceptable inorganic salt, pharmaceutically acceptable organic salt, morphine hydrobromide, morphine hydrochloride, morphine mucate, morphine N-oxide, morphine sulfate, morphine acetate, morphine phosphate dibasic, morphine phosphate monobasic, morphine inorganic salt, morphine organic salt, morphine acetate trihydrate, morphine bi(heptafluorobutyrate), morphine bi(methylcarbamate), morphine bi(pentafluoropropionate), morphine bi(pyridine-3-carboxylate), morphine bi(trifluoroacetate), morphine bitartrate, morphine chlorhydrate, and morphine sulfate pentahydrate, and 600 g of an analgesic selected from the group consisting of acetaminophen, aspirin, benoxaprofen, flurbiprofen, ibuprofen, indoprofen, propoxyphene, salicylamide, zenazocrine and zomepirac are blended with 963 g of poly (alkylene oxide) comprising a 300,000 molecular weight and 90 g of poly(vinyl pyrrolidone) having an average molecular weight of 40,000 are added to a mixing bowl and dry mixed for 12 minutes. Next, 404 g of denatured, anhydrous alcohol is slowly added to the blended composition forming materials with continuous mixing for 15 minutes. Then, the prepared granulation is passed through a 20 mesh screen, and allowed to dry at 25° C. for 18 hrs, and then passed through a 16 mesh screen. The screened granulation is transferred to a planetary mixer, and with constant blending 14.9 g of calcium stearate is added to produce the therapeutic two analgesic composition. The composition is compressed into tablets comprising 350 mg of the therapeutic composition consisting of 70 mg of opioid analgesic and 100 mg of nonopioid analgesic and 180 mg of tablet forming materials. The tablets are compressed under 2.5 tons of pressure to provide a sustained release analgesic tablet.

EXAMPLE 7

The therapeutic compositions provided above and comprising the opioid analgesic and the nonopioid analgesic are

coated with a biwall comprising an interior wall, and exterior wall and an exit passage by following the procedure of Example 2 to provide a controlled-linear-extended zero-releasing dosage form indicated for the management of pain.

EXAMPLE 8

A controlled release dosage form for once a day administration of the potent opioid analgesic, morphine, was fabricated as follows: First, 350 grams of morphine sulfate hexahydrate, 585 grams of polyoxyethylene having a molecular weight of approximately 200,000 grams per mole, and 60 grams of polyvinyl pyrrolidone having a molecular weight of 40,000 grams per mole were each passed through a stainless screen having 40 wires per inch and then dry mixed. Anhydrous ethanol was added with mixing until a uniform damp mass formed. The damp mass was forced through a screen having 20 wires per inch, forming granules which were then air dried at 22.5° C. overnight. After drying the granules were passed again through the 20 mesh screen forming free-flowing granules. Then, 4.5 grams of magnesium stearate and 0.5 grams of butylated hydroxytoluene were passed through a screen with 60 wires per inch into the granules. The resulting mixture was tumbled for 5 minutes to form a homogenous blend, to produce a drug granulation.

In a separate process, 936.7 grams of polyoxyethylene having a molecular weight of approximately 7 million grams per mole, 50 grams of hydroxypropyl methyl cellulose having a molecular weight of 11,300 grams per mole and a hydroxypropyl content of 10 weight percent and a methoxyl content of 29 weight percent, were individually passed through a screen with a size of 40 wires per inch. Then, 10 grams of ferric oxide green and 0.8 grams of butylated hydroxytoluene were passed through a screen with 60 wires per inch into the bulk mixture. The resulting powders were mixed to a uniform blend. Then, anhydrous ethanol was added with mixing to produce a uniform damp mass. The damp mass was then forced through a screen with 20 wires per inch and air dried at ambient room conditions, 22° C., overnight. The dried granules were then forced through the 20 mesh screen. Finally, 2.5 grams of magnesium stearate, 0.8 grams of butylated hydroxytoluene were passed through a screen with 60 wires per inch into the granules. The mixture was tumble mixed for 3 minutes to produce a push-displacement composition.

Next, bilayer tablets, comprising the morphine composition, and the push-displacement composition, were compressed on a bilayer-tablet press with the above granulations using a $^{13}/_{32}$ inch (10.3 mm) round tooling punch. First, 287 mg of drug granulation was fed into the die cavity and lightly compacted. Then, 151 mg of the push granulation was added to the die cavity and laminated to the push layer with a force of 0.4 tons. Each of the resulting tablets contained a unit doses of 100 mg morphine sulfate pentahydrate.

Next, the bilayer cores, prepared immediately above, were then coated with the laminated membrane of this invention according to the following procedures: First, 154 grams of ethyl cellulose having a molecular weight of approximately 220,000 grams per mole and an ethoxyl content of 48.0 to 49.5 weight percent, 112 grams of hydroxypropyl cellulose having a molecular weight of 80,000 and a molar substitution of 3 and 14 grams of polyoxyethylene (40) stearate was dissolved in 3,720 grams of anhydrous ethanol formula with stirring. The resulting solution was allowed to stand without stirring for 3 days. This solution is referred to as the interior wall forming solution. A second solution was prepared by dissolving 162.5 grams of cellulose acetate having a acetyl content of 39.8 weight percent and an approximate molecular weight of 40,000 grams per mole and 87.5 grams of ethylene oxide-propylene oxide-ethylene oxide triblock copolymer having molecular weight of approximately 8,600 grams per mole and an ethylene oxide content of 82 weight percent in 4,750 grams of anhydrous acetone with stirring and slight warming to 26 degrees centigrade. The resulting solution is the exterior-wall forming solution and it was allowed to stand at ambient room temperature for one day.

The tablets were then charged into a pan coater. The interior-wall forming solution was sprayed onto the tablets in a current of warm air until a coating thickness of 9 mils was applied. The coating solution was stirred continuously while the tablets were being coated. The coated tablets were then removed from the coating pan and dried in a forced air oven thermostated to 40 degrees centigrade for a day. Then, the tablets were returned to the pan and the exterior wall forming solution was sprayed onto the dried tablets until a coating thickness of 3 mils was applied. The exterior wall forming solution was stirred continuously during the coating process. After coating the tablets were removed from the coater and a delivery orifice was drilled through the laminated walls with a drill bit producing one round port having a diameter of 25 mils in the center of the drug layer side of the tablet. The drilled systems were then placed in a forced air drying oven thermostated to 50 degrees centigrade for 3 days which drying completed the fabrication of the dosage form.

The dose release performance of the dosage forms prepared according to this example were ascertained by measuring the dose release in distilled water at 37° C. and as seen in the delivery pattern of drawing FIG. **6**. The measured results indicated a linear profile over 12 hrs at a constant rate of release of about 6 mg/hr during the corresponding time period.

The dosage form prepared according to this example with the results depicted in FIG. **6** comprises: a drug layer composition comprising 35 wt % morphine sulfate pentahydrate, 58.50 wt % poly(ethylene oxide) possessing a 200,000 molecular weight, 6 wt % poly(vinyl pyrrolidone) of 40,000 molecular weight, 0.45 wt % magnesium stearate, and 0.05 wt % butylated hydroxytoluene; a push-displacement composition comprising 93.67 wt % poly (ethylene oxide) possessing a 7,000,000 molecular weight, 5 wt % hydroxypropylmethylcellulose possessing a 11,200 molecular weight, 1 wt % green ferric oxide, 0.25 wt % magnesium stearate, and 0.08 wt % butylated hydroxytoluene; an interior wall comprising 55 wt % ethylcellulose possessing a viscocity of 100 centipoises, 40 wt % hydroxypropylcellulose of 80,000 molecular weight, and 5 wt % Myrj 52S manufactured by ICI Americas, Inc., Wilmington, Del. which represents polyoxyethylene (40) stearate; an exterior wall comprising 65 wt % cellulose acetate possessing a 39.8% acetyl content, and 35 wt % Pluronic F68 manufactured by BASF Corporation, Mt. Olive, N.J., which represents a triblock copolymer of ethylene oxide-propylene oxide-ethylene oxide having a molecular weight of approximately 8,400 grams per mole with approximately 82 weight percent ethylene oxide content; a nominal time to deliver 80% of dose of 15.7 hrs; a mean release rate of 6.4 mg/hr; an exit port of 25 mil (0.635 mm), and a dose of drug of 100 mg; with the drug composition weighing 287 mg; the push-displacement composition 151 mg, the interior wall 80.1 mg; and the exterior wall 26.9 mg; the interior wall was 8.8 mil (0.224 mm) thick and the exterior wall 2.6 mil (0.066 mm) thick.

EXAMPLE 9

The present example is provided to illustrate the unexpected results obtained by this example. The dosage form of this example comprises a single wall. The dosage form drug composition comprises the identical core composition as specified in Example 8 which is 35 wt % morphine sulfate pentahydrate, 58.50 wt % polyethylene oxide possessing a 200,000 molecular weight, 6 wt % polyvinyl pyrrolidone possessing a 40,000 molecular weight, 0.45 wt % magnesium stearate, and 0.05 wt % butylated hydroxytoluene; a push-displacement composition comprising 93.97 wt % polyethylene oxide possessing a 7,000,000 molecular weight, 5 wt % hydroxypropylmethylcellulose possessing a 11,200 molecular weight, 1 wt % green ferric oxide, 0.25 wt % magnesium stearate, and 0.08 wt % butylated hydroxytoluene; a single wall comprising 92.0 wt % cellulose acetate possessing a 39.8% acetyl content, and 8 wt % polyethylene glycol possessing a 3350 molecular weight; and a mean release rate of 6.6 mg/hr. The single wall was formed from 80:20(v:v) methylene oxide: methanol. The results disputed in drawing FIG. **7** indicated the dosage form delivered drug for 16 hours at a nonzero order continuously declining rate.

EXAMPLE 10

The procedure set forth above was followed to manufacture a dosage form with a drug composition comprising 35 wt % morphine sulfate pentahydrate, 58.5 wt % polyethylene oxide possessing a 200,000 molecular weight, 6.0 wt % polyvinyl pyrrolidone of 40,000 molecular weight, 0.45 wt % magnesium stearate, and 0.05 butylated hydroxytoluene; a push-displacement composition comprising 93.97 wt % polyethylene oxide possessing a 7,000,00 molecular weight, 5.0 wt % hydroxypropylmethylcellulose possessing a 11,200 molecular weight, 1 wt % green ferric oxide, 0.25 wt % magnesium stearate, and 0.08 wt % butylated hydroxytoluene; an inside wall comprising 55 wt % ethyl cellulose having an ethoxyl content in the range of 48.0 to 49.5 weight percent and a viscosity of 100 centipoise as a 5 percent solution at 25° centigrade in 80:20 toluene:ethanol, 20 wt % hydroxypropylcellulose of molecular weight 80,000 grams per mole as supplied as Klucel® EF manufactured by Hercules Inc., Wilmington, Del., 20 wt % Kollidon 12 PF polyvinylpyrrolidone manufactured by BASF, Ludwigshaften, West Germany, and 5 wt % Myrj 52S of approximately 2,060 grams per molecular weight (see Example 8); an outside wall comprising 65 wt % cellulose acetate having a 39.8% acetyl content, and 35 wt % Pluronic F68 (see Example 8); one 25 mil (0.635 mm) exit; and a mean release rate of 6.4 mg/hr. The dosage form provided by this example exhibits the drug release profile seen in FIG. **8**. The dosage form delivers drug at substantially zero orderate earlier than the dosage form disclosed in Example 4 and its delivery profile attributed to the increase of pore forming polyvinyl pyrrolidone in the interior wall.

EXAMPLE 11

The present example provide a delivery system for delivering a narcotic analgesic manufactured according to the examples set forth above, with the drug delivered from the present example a member selected from the group consisting of oxymorphone, hydromorphone, metopon, hydrocodone, levorphanol, phenazocine, methadone, dextromoramide, dipipanone, phenadoxone, codeine, dihydrocodeine, oxycodone, pholcodine, meperidine, levorphanol, phenazocine, methadone, dextromoramide, dipanone, phenodozone, meperidine, alphaprodine, anileridine, and pimiondone.

EXAMPLE 12

An osmotic dosage form designed to deliver morphine at extended zero order rate was fabricated as follows. 330 grams of morphine sulfate hexahydrate and 610 grams of mannitol were dry blended and then passed through a screen with 40 wires per inch into the bowl of a planetary mixer. 50 grams of polyvinyl pyrrolidone having a molecular weight of 9,000 grams per mole was dissolved with stirring in 500 milliliters of anhydrous ethyl alcohol to form a binder solution. The binder solution was added slowly to the powders as they were mixed in the planetary mixer until a damp mass was formed. The damp mass was then passed through a screen with 20 wires per inch. The resulting extrusions were air dried overnight at room temperature and then passed again through a 20 mesh screen, thereby forming free-flowing granules. 10 grams of magnesium stearate sized through a 60 mesh screen was then tumble mixed into the granules producing the finished granulation. The resulting granulation was compressed with a force of 1.5 tons using with 11/32 round standard concave tooling at a tablet weight 304 mg. Each tablet contained a unit dose equivalent to 100 mg of morphine sulfate hexahydrate.

The tablets were then coated with an interior wall consisting of 55 parts by weight of ethylcellulose having a molecular weight of 220,000 grams per mole, 30 parts by weight of hydroxypropyl cellulose having a molecular weight of 80,000, 5 parts by weight of hydroxypropyl cellulose having a molecular weight of 300,000, 5 parts of polyvinyl pyrrolidone molecular weight having a molecular weight of 1,300 grams per mole and 5 parts of the ethylene oxide-propylene oxide-ethylene oxide triblock copolymer having a nominal molecular weight of 7,700 grams per mole with 72 weight percent of ethylene oxide supplied by BASF Corporation as Pluronic F87. This composition was applied from a solution of ethyl alcohol according to the procedures outlined in Example 8 to a thickness of 5 mils. Then, an exterior wall was applied according to the procedures in Example 8 by spray coating 3 mils of 70 parts cellulose acetate having an acetyl content of 39.8 weight percent and 40,000 grams per mole and 30 parts polyethylene glycol having a molecular weight of 400 from a solution of acetone. Two delivery ports were then drilled in the system, one per side, centered in the round dome of the dosage form. Finally, the dosage form was dried for 3 days at 50° centigrade to remove residual coating solvents and establish equilibrium composition of the coating. This resulted in a dosage form which when placed in an aqueous environment generated a internal osmotic pressure of 46 atmospheres which remained constant while solid drug was present within the core. After the last bit of solid drug was dissolved, the osmotic pressure within the core declined to less than 30 atmospheres thereby allowing the pore formers of the internal wall to elute from the wall, thereby increasing wall permeability to compensate for the decreasing in osmotic driving force with the net effect to maintain elevated rate of release of the analgesic for prolonged time.

EXAMPLE 13

A dosage form which delivers the analgesic hydromorphone for once daily administration was fabricated as follows: 28.6 grams of hydromorphone hydrochloride and 50 grams of polyvinyl pyrrolidone having a molecular weight of 2,500 grams per mole were dissolved with stirring in 500 milliliters of ethyl alcohol. 914 grams of sodium chloride was dried at 50° C. in forced air overnight and then was passed through a sieve with 40 wires per inch into a

planetary mixer. The solution of drug was then slowly added to the sodium chloride powder with stirring to form a uniform damp mass. Two washings of ethanol were performed to complete the quantitative transfer of the drug into the damp mass. The damp mass was then passed through a mesh with 20 wires per inch, spread on a tray, and then oven dried overnight in forced air at 40° C. The dried material was then passed through a screen with 20 wires per inch, forming a free flowing mixture. Finally, 7 grams of stearic acid was passed through a screen with 80 wires per inch into the bulk mixture and tumble mixed for 3 minutes, completing the granulation. The resulting granulation was compressed at a force of 2 tons using ⅜ inch (9.5 mm) diameter round tooling at a tablet weight of 280 milligrams. Each tablet contained a unit dose of 8 milligrams of the analgesic.

The tablets were then coated with an interior wall composition consisting of 55 parts of ethylcellulose having a molecular weight of approximately 118,000 grams per mole and an ethoxyl content of 48.0–49.5 weight percent, 40 parts of the osmotically-sensitive pore former methyl cellulose having a molecular weight of approximately 10,400 grams per mole as supplied by the Dow Chemical Company, Midland, Mich. in Methocel™ A5, and 5 parts polyoxyethylene (50) stearate. The coating fluid to apply this composition was prepared by dissolving the ethyl cellulose and the polyoxyethylene (50) stearate in ethyl alcohol and then dispersing the methyl cellulose in the resulting solution. The resulting fluid was spray coated according to the procedures in Example 8 to a wall thickness of 6 mils. Then, the exterior wall consisting of 85 parts cellulose acetate with an acetyl content of 39.8 weight percent and a molecular weight of approximately 50,000 grams per mole and 15 parts of the ethylene oxide-propylene oxide-ethylene oxide triblock copolymer having a molecular weight of approximately 8,600 grams per mole and a ethylene oxide content of 82 weight percent otherwise referred to as Pluronic F87 were applied from a solution of acetone according to the procedures in Example 8 to a uniform exterior wall thickness of 3 mils. Then, a 15 mil diameter port was laser drilled through both walls in the center of each side of the dosage from. Finally, the residual coating solvents were removed by drying in forced air with 50% relative humidity at a temperature of 50° C. for 48 hours followed by four hours at 50° C. without humidity.

When placed in an aqueous environment, water is imbibed by osmosis into the dosage form dissolving the drug and salt to produce an internal osmotic pressure of 287 atmospheres and an ionic strength of 5.47 molar which osmotic pressure and ionic strength is maintained while the drug is dispensed until the last remaining portion of sodium chloride dissolves, at which point in time, the sodium chloride dilutes as a result of the water continuing to flow into the dosage form to lower levels of osmotic pressure and ionic strength, thereby allowing the pore former within the interior wall to dissolve and elute from the wall and thus increase permeability of the wall to compensate for the decrease in osmotic pressure as a result of the dilution. The dosage form meters the release of 8 milligrams of the analgesic at controlled rate over prolonged time.

EXAMPLE 14

An extended release dosage form of the analgesic hydrocodone for dosing once a day dosing was prepared. 6,000 grams of hydrocodone bitartrate hemipentahydrate and 19,000 grams of the osmotic agent glycine were individually milled to a particle size of less than 420 microns and charged into a fluid bed granulator. Then, a binder solution was prepared by dissolving of 130 grams of hydroxypropyl methylcellulose having a hydroxypropyl content of 10 weight percent, a methoxyl content of 29 weight percent and a molecular weight of 11,300 grams per mole as supply under the product name Methocel E5 manufactured by DOW Chemical Company, Midland, Mich., in 2,470 milliliters of distilled water with stirring. The powders fluidized in a current of air and then the binder solution was sprayed onto the fluidized powders in a current of warm air until to form granules. The granules were removed from the granulator and transferred to a tote mixer where 30 grams of tablet lubricant, hydrogenated vegetable oil, was passed through a mesh with 60 wires per inch into the bulk granulation. The lubricant was mixed into the bulk by tumbling for 3 minutes. The resulting granulation was compressed with oval tooling at a compression force of 2 tons to an average tablet weight of 252 milligrams. Each tablet contained a unit dose of 60 milligrams of the analgesic.

The resulting tablets were coated according to the procedures described in Example 8. The interior wall consisted of 60 parts ethylcellulose having an ethoxyl content of 48.0–49.5 with a molecular weight of approximately 78,000 grams per mole, 34 parts hydroxypropyl cellulose having a molecular weight of approximately 80,000 grams per mole, 1 part dibutyl sebaccate, and 5 parts polyoxyethylene (8) stearate as supplied in Myrj 45 manufactured by ICA Americas, sprayed from ethyl alcohol to a coating thickness of 6.5 mils. The exterior wall was applied according to the procedures detailed in Example 8. The coating consisted of 90 parts cellulose acetate having an acetyl content of 39.8 weight percent and an average molecular weight of 30,000 grams per mole and 10 parts of ethylene oxide-propylene oxide-ethylene oxide triblock copolymer having an ethylene oxide content of 83 weight percent and a molecular weight of 14,600 grams per mole sprayed from acetone at 2.5 weight percent in the acetone to an exterior wall thickness of 2.5 mils. A 15-mil diameter delivery port was then laser drilled on both sides of the dosage from. Fabrication was completed by drying in a forced air oven at 50° C. in forced air for 3 days to remove residual solvents.

When the resulting dosage form was placed in aqueous media, it imbibed water across the bilayer wall coating under the osmotic gradient across the membrane where the internal osmotic pressure was 90 atmospheres was maintained while solid drug and glycine were present, after which point, the osmotic pressure continuously declined in time. This process continued until the internal osmotic pressure declined to below 30 atmospheres at which point the osmotically-sensitive pore former hydroxypropyl cellulose eluted from the interior wall, thereby increasing the permeability to compensate for the continuously decreasing osmotic driving force. The resulting dosage form delivered 60 mg of the analgesic at controlled rate over prolonged time.

METHOD OF PRACTICING INVENTION

The invention pertains additionally to the use of the therapeutic dosage form by providing a method for delivering a drug orally to a warm-blooded animal including a human patient in need of therapy. The method comprises administering orally the therapeutic dosage form into the patient, wherein the dosage form comprises a therapeutic composition surrounded by an interior wall and a contacting outside wall, or the method comprises administering a dosage form comprising a therapeutic composition and a push composition with both compositions surrounded by an inside wall and an outside wall. The dosage form, in both methods of use, in the gastrointestinal tract imbibes fluid

through both wall, generates osmotic energy, that causes the therapeutic composition to be administered through an exit port up to 24 hours to provide controlled and sustained therapy.

In summary, it will be appreciated that the present invention contributed to the art an unobvious dosage form that possesses practical utility, and can administer a drug at a dose-metered release rate per unit time. While the invention has been described and pointed out in detail with reference to operative embodiments thereof, it will be understood by those skilled in the art that various changes, modifications, substitution and omissions can be made without departing from the spirit of the invention. It is intended, therefore, that the invention embrace those equivalents within the scope of the claims which follow.

What is claimed is:

1. A therapeutic solid, sustained-release composition comprising a member selected from the group consisting of hydromorphone and its pharmaceutically acceptable salts, acetaminophen, and a pharmaceutically acceptable polyethylene oxide carrier.

2. The therapeutic composition according to claim **1**, wherein the composition comprises polyvinylpyrrolidone.

3. A therapeutic solid, sustained-release composition comprising a member selected from the group consisting of hydromorphone and its pharmaceutically acceptable salts, acetaminophen, and a pharmaceutically acceptable polyethylene oxide carrier, which composition is coated with a wall comprising ethylcellulose and hydroxypropylcellulose.

4. A therapeutic solid, sustained-release composition comprising a member selected from the group consisting of hydromorphone and its pharmaceutically acceptable salts, acetaminophen, and a pharmaceutically acceptable polyethylene oxide carrier, which composition is coated with an interior wall comprising ethyl cellulose and hydroxypropylcellulose and an exterior wall comprising cellulose acetate.

5. A therapeutic solid, sustained-release composition comprising an opioid analgesic and a nonopioid analgesic, wherein the opioid analgesic comprises 0.1 μg to 1000 mg of a member selected from the group consisting of hydromorphone and its pharmaceutically acceptable salts, the nonopioid analgesic comprises 1 mg to 1000 mg of a member selected from the group consisting of aspirin, flurbiprofen, ibuprofen, indoprofen, benoxaprofen, salicylamide, zenazocine and zomepirac, and 10 mg to 500 mg of a pharmaceutically acceptable poly(alkylene oxide) carrier.

6. The therapeutic composition according to claim **5**, wherein the poly(alkylene oxide) is replaced by a pharmaceutically acceptable carboxyalkylcellulose carrier.

7. The therapeutic composition according to claim **5**, wherein the composition is coated with a wall comprising ethylcellulose and hydroxypropylcellulose.

8. The therapeutic composition according to claim **5**, wherein the composition is coated with a wall comprising cellulose acylate.

9. The therapeutic composition according to claim **5**, wherein the composition comprises a polyvinylpyrrolidone.

10. A therapeutic solid, sustained-release composition comprising a first analgesic selected from the group consisting of morphine and its pharmaceutically acceptable salts, a second analgesic selected from the group consisting of acetaminophen, aspirin, benoxaprofen, flurbiprofen, ibuprofen, indoprofen, salicylamide, zenazocine, and zomepirar, and a pharmaceutically acceptable poly(alkylene oxide) carrier.

11. The therapeutic composition according to claim **10**, wherein the poly (alkylene oxide) is replaced by a pharmaceutically acceptable carrier.

12. The therapeutic composition according to claim **10**, wherein the composition is coated with a wall comprising ethylcellulose and hydroxypropylcellulose.

13. The therapeutic composition according to claim **10**, wherein the composition is coated with a wall comprising a cellulose acetate.

14. The therapeutic composition according to claim **10**, wherein the composition is a dosage form tablet and comprises 1 mg to 1000 mg of the first analgesic and 1 mg to 1000 mg of the second analgesic.

15. A laminate for manufacturing a dosage form, the laminate comprising a lamina comprising ethylcellulose and hydroxypropylcellulose, and a lamina comprising cellulose acetate.

16. A dosage form tablet comprising a drug coated with a laminate comprising a lamina comprising ethylcellulose and hydroxypropylcellulose and a lamina comprising cellulose acetate.

17. A dosage form tablet comprising a drug, an interior wall in contact with tablet comprising ethylcellulose and hydroxypropylcellulose, and an exterior wall in contact with the interior wall comprising cellulose acetate.

18. A dosage form composition comprising 35 wt % morphine sulfate pentahydrate, 58.50 wt % poly(ethylene oxide), 6 wt % poly(vinylpyrrolidone), 0.45 wt % magnesium stearate, and 0.05 wt % butylated hydroxytoluene; and a wall comprising ethylcellulose and hydroxypropylcellulose in contact with the composition, and a wall comprising cellulose acetate distant from the composition.

19. A dosage form comprising a drug composition, an expandable composition, an interior wall in contact with both composition comprising an ethylcellulose and a hydroxypropylcellulose, and an exterior wall in composition with the interior wall comprising a cellulose acylate.

20. A dosage form comprising a drug layer comprising 35 wt % morphine sulfate pentahydrate, 58.50 wt % polyethylene oxide, 6 wt % polyvinylpyrrolidone, 0.45 wt % magnesium stearate, and 0.05 wt % butylated hydroxytoluene; a push-displacement layer comprising 93.97 wt % polyethylene oxide, 5 wt % hydroxypropylmethylcellulose, 1 wt % ferric oxide, 0.25 wt % magnesium stearate, and 0.08 wt % butylated hydroxytoluene; and a wall surrounding the layers comprising 92 wt % cellulose acetate and 8 wt % polyethylene glycol.

21. A dosage form comprising a drug layer comprising 35 wt % morphine sulfate pentahydrate, 58.5 wt % polyethylene oxide, 6.0 wt % polyvinylpyrrolidone, 0.45 wt % magnesium stearate, and 0.05 wt % butylated hydroxytoluene; a push displacement layer comprising 93.97 wt % polyethylene oxide, 5.0 wt % hydroxypropylmethylcellulose, 1 wt % green ferric oxide, 0.25 wt % magnesium stearate, and 0.08 wt % butylated hydroxytoluene; an inside wall that surrounds the layers comprising ethylcellulose, hydroxypropylcellulose and polyvinylpyrrolidone; an outside wall that surrounds the inside wall comprising cellulose acetate and a surfactant; and an exit in the walls for releasing the morphine from the dosage form.

22. A method of administering a unit dose of opioid analgesic to a patient in need of opioid analgesia, where in the method comprises administering zero to 15 percent of the dose for zero hours to four hours, then 15 percent to 55 percent of the dose for four hours to eight hours, 55 percent to 75 percent of the dose for eight to twelve hours, and 75 percent to 100 percent of the unit dose for twelve hours to twenty-four hours.

23. A method of administering a dose of an opioid analgesic to a patient in need of an opioid analgesic, wherein

the method comprises administering to the patient a dosage form tablet comprising 1 mg to 1000 mg of an opioid analgesic that is administered in a dose of 2 mg to 8 mg from zero hours to eighteen hours and 2 mg to zero mg from eighteen hours to twenty-four hours for administering the opioid analgesic to the patient.

24. A process for increasing the rate of drug released from a dosage form, wherein the process comprises: enveloping a dose of drug with a wall comprising a passage-former that, in the presence of fluid, leaves the wall and lets more fluid into the dosage form for increasing the release of drug over a sustained-release period up to twenty-four hours from the dosage form; and enveloping the wall with a different wall that provides support to the dosage form.

25. A process for maintaining an extended-linear, non-declining release drug profile from a dosage form comprising a core of drug, wherein the process comprises: coating a core comprising a drug with a composition comprising a passage former that, leaves the composition in the presence of fluid and correspondingly make available an increase in passages that increase fluid inflow into the dosage form over time; and, coating the coated composition with a coat that provides fluid to the coated composition, whereby through the coat and the coated composition, the dosage form maintains the delivery over time.

26. A dosage form for delivering a drug at a sustained-release rate to a gastrointestinal-lipid-fluid environment of use, wherein the dosage form comprises: a composition comprising a dose of drug; a coat that envelopes the composition comprising the drug, which coat comprises a passage-former that leaves the coat in the presence of fluid; and a wall that surrounds the coat and prevents lipid in the gastrointestinal tract from entering the dosage form.

27. The dosage form according to claim **26**, wherein the coat lets an increasing volume of fluid into the coated composition comprising the drug.

28. A membrane system comprising: an internal compartment defined by said membrane system; an interior wall surrounding the internal compartment, wherein fluid permeability of said interior wall is responsive to osmolarity of an osmotic core comprised in said internal compartment; and a fluid-permeable exterior wall surrounding the interior wall.

29. The membrane system of claim **28** wherein the interior wall and the exterior wall are in contacting relationship.

30. The membrane system of claim **28** wherein the fluid permeability of said interior wall increases in response to a decrease in the osmolarity of the osmotic core.

31. The membrane system of claim **28**, wherein said interior wall comprises a hydrophobic substance and a hydrophilic substance, and said exterior wall is semipermeable.

32. The membrane system of claim **31** wherein the hydrophilicity of the hydrophilic substance is osmosensitive.

33. The membrane system of claim **31**, wherein said hydrophilic substance exhibits an aqueous solubility responsive to osmotic pressure and/or ionic strength of said osmotic core.

34. The membrane system of claim **33**, wherein the hydrophilic substance provides increased permeability of the interior wall in response to a decrease in the osmotic pressure and/or the ionic strength of said osmotic core.

35. The membrane system of claim **31**, wherein said hydrophobic substance comprises ethyl acetate or cellulose acetate; said hydrophobic membrane comprises hydroxyalkylcellulose; and said semipermeable substance comprises cellulose acetate.

36. The membrane system of claim **28**, wherein said internal compartment comprises a therapeutic agent.

37. The membrane system of claim **36**, wherein said internal compartment comprises a pharmaceutically acceptable osmotically-effective compound.

38. The membrane system of claim **37**, wherein said internal compartment comprises a pharmaceutically acceptable hydrogel polymer.

39. The membrane system of claim **37**, wherein said hydrophilic substance exhibits an aqueous solubility responsive to osmotic pressure and/or ionic strength of said osmotic core.

40. The membrane system of claim **37**, wherein said hydrophilic substance exhibits an aqueous solubility responsive to said osmotically-effective compound.

41. The membrane system of claim **36**, wherein said internal compartment further comprises an expandable layer.

42. The membrane system of claim **41**, wherein said expandable layer comprises an osmotically-effective compound.

43. The membrane system of claim **42**, wherein said interior wall comprises a hydrophilic substance.

44. The membrane system of claim **43**, wherein said hydrophilic substance exhibits an aqueous solubility responsive to osmotic pressure and/or ionic strength of said osmotic core.

45. The membrane system of claim **43**, wherein said hydrophilic substance exhibits an aqueous solubility responsive to said osmotically-effective compound.

46. A controlled release dosage form comprising:

an osmotic core,

an interior wall surrounding at least a portion of said core osmotic core, wherein fluid permeability of the interior wall is responsive to osmolarity of said osmotic core; and

a fluid-permeable exterior wall surrounding the interior wall.

47. A controlled release dosage form comprising:

an osmotic core,

an interior wall in contact with the osmotic core, wherein fluid permeability of the interior wall is responsive to osmolarity of said osmotic core; and

a fluid-permeable exterior wall in contact with the interior wall.

48. The controlled release dosage form of claim **46** wherein said osmotic core comprises a therapeutic agent.

49. The controlled release dosage form of claim **48** wherein the osmotic core, the internal wall and the external wall act in concert to provide a controlled delivery of said therapeutic agent over an extended or sustained-release period of time.

50. The controlled release dosage form of claim **49**, wherein said therapeutic agent is delivered over a period of about 30 minutes to about 24 hours.

51. The controlled release dosage form of claim **50**, wherein said therapeutic agent is delivered over a period of about 4 hours to about 24 hours.

52. The controlled release dosage form of claim **46**, wherein said interior wall comprises a hydrophobic substance and a hydrophilic substance, and said exterior wall is semipermeable.

53. The controlled release dosage form of claim **52** wherein the hydrophilicity of the hydrophilic substance is osmosensitive.

54. The controlled release dosage form of claim **52**, wherein said hydrophilic substance exhibits an aqueous

solubility responsive to osmotic pressure and/or ionic strength of said osmotic core.

55. The controlled release dosage form of claim **52**, wherein hydrophilic substance provides increased permeability of the interior wall in response to a decrease in the osmotic pressure and/or the ionic strength of said osmotic core.

56. The controlled release dosage form of claim **52**, wherein said hydrophobic substance comprises ethyl acetate or cellulose acetate; said hydrophobic membrane comprises hydroxyalkylcellulose; and said semipermeable substance comprises cellulose acetate.

57. A process for delivering an osmotically active formulation from an osmotic pump over an extended period of time comprising:

(i) disposing said formulation in an osmotic pump;

(ii) exposing said osmotic pump to a fluid environment to cause delivery of said formulation therefrom in response to osmotic imbibition of fluid into said pump; and

(iii) increasing the fluid permeability of said pump in response to decreasing osmolarity of said formulation.

58. The process of claim **57** wherein said formulation comprises a therapeutic agent.

59. The process of claim **58** wherein said therapeutic agent is delivered in an extended-linear, non-declining release profile over a period of about 30 minutes to about 24 hours.

60. The process of claim **59** wherein said therapeutic agent is delivered in an extended-linear, non-declining release profile over a period of about 4 hours to about 24 hours.

61. The process of claim **59** wherein said extended-linear release profile is a zero order release profile.

62. The process of claim **59** wherein said extended-linear release profile is an ascending release profile.

63. A membrane comprising a semipermeable membrane having a control membrane disposed thereon, the water permeability of said control membrane being responsive to changes in the osmolarity of fluid contacting said control membrane.

64. The membrane of claim **63** wherein the water permeability of the control membrane is inversely proportional to changes in the osmolality of fluid contacting said control membrane.

65. An osmotic pump comprising:

an osmotic core;

a semipermeable membrane enclosing at a least a portion of said core; and

a control membrane disposed between at least a portion of said semipermeable membrane and said core, the water permeability of said control membrane being responsive to changes in the osmolarity of said core.

66. The osmotic pump of claim **65** wherein the water permeability of the control membrane is inversely proportional to changes in the osmolarity of said core.

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